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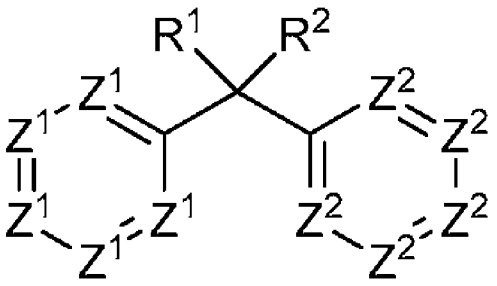
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

[Continued on next page]

(54) Title: DIBENZYLPHENYL COMPOUNDS AND METHODS FOR THEIR USE



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(57) Abstract: Compounds having a structure of Formula I: or a pharmaceutically acceptable salt thereof, wherein Z^1, Z^2, R^1 and R^2 are as defined herein are provided. Uses of such compounds for treatment of various indications, including prostate cancer as well as methods of treatment involving such compounds are also provided.

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DIBENZYLPHENYL COMPOUNDS AND METHODS FOR THEIR USE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Patent Application No. 61/476,729 filed 18 April 2011, where this provisional application is incorporated herein by reference in its entirety.

FIELD OF INVENTION

This invention relates to therapeutics, their uses and methods for the treatment of various indications, including various cancers. In particular the invention relates to therapies and methods of treatment for cancers such as prostate cancer, including all stages and androgen dependent, androgen-sensitive and castration-resistant (also referred to as hormone refractory, androgen-independent, androgen deprivation resistant, androgen ablation resistant, androgen depletion-independent, castration-recurrent, anti-androgen-recurrent).

BACKGROUND OF THE INVENTION

Androgens mediate their effects through the androgen receptor (AR). Androgens play a role in a wide range of developmental and physiological responses and are involved in male sexual differentiation, maintenance of spermatogenesis, and male gonadotropin regulation (R. K. Ross, G. A. Coetzee, C. L. Pearce, J. K. Reichardt, P. Bretsky, L. N. Kolonel, B. E. Henderson, E. Lander, D. Altshuler & G. Daley, *Eur Urol* 35, 355-361 (1999); A. A. Thomson, *Reproduction* 121, 187-195 (2001); N. Tanji, K. Aoki & M. Yokoyama, *Arch Androl* 47, 1-7 (2001)). Several lines of evidence show that androgens are associated with the development of prostate carcinogenesis. Firstly, androgens induce prostatic carcinogenesis in rodent models (R. L. Noble, *Cancer Res* 37, 1929-1933 (1977); R. L. Noble, *Oncology* 34, 138-141 (1977)) and men receiving androgens in the form of anabolic steroids have a higher incidence of prostate cancer (J. T. Roberts & D. M. Essenhigh, *Lancet* 2, 742 (1986); J. A. Jackson, J. Waxman & A. M. Spiekerman, *Arch Intern Med* 149, 2365-2366 (1989); P. D. Guinan, W. Sadoughi, H. Alsheik, R. J. Ablin, D. Alrenga & I. M. Bush, *Am J Surg* 131, 599-600 (1976)). Secondly, prostate cancer does not develop if humans or dogs are castrated before

puberty (J. D. Wilson & C. Roehrborn, *J Clin Endocrinol Metab* 84, 4324-4331 (1999); G. Wilding, *Cancer Surv* 14, 113-130 (1992)). Castration of adult males causes involution of the prostate and apoptosis of prostatic epithelium while eliciting no effect on other male external genitalia (E. M. Bruckheimer & N. Kyprianou, *Cell Tissue Res* 301, 153-162 (2000); J. T. Isaacs, *Prostate* 5, 545-557 (1984)). This dependency on androgens provides the underlying rationale for treating prostate cancer with chemical or surgical castration (androgen ablation).

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

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

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

Available inhibitors of the AR include nonsteroidal antiandrogens such as bicalutamide (Casodex™), nilutamide, flutamide, investigational drugs MDV3100 and ARN-509, and the steroidal antiandrogen, cyproterone acetate. These antiandrogens target the LBD of the AR and predominantly fail presumably due to poor affinity and 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., *Cancer Res*., 59, 2511-2515 (1999)). These antiandrogens would also have no effect on the recently discovered AR splice variants that lack the ligand-binding domain (LBD) to result in a constitutively active receptor which promotes progression of androgen-independent prostate cancer (Dehm SM, Schmidt LJ, Heemers HV, Vessella RL, Tindall DJ., *Cancer Res* 68, 5469-77, 2008; Guo Z, Yang X, Sun F, Jiang R, Linn DE, Chen H, Chen H, Kong X, Melamed J, Tepper CG, Kung HJ, Brodie AM, Edwards J, Qiu Y., *Cancer Res*. 69, 2305-13, 2009; Hu et al 2009 Cancer Res. 69, 16-22; Sun et al 2010 J Clin Invest. 2010 120, 2715-30).

Conventional therapy has concentrated on androgen-dependent activation of the AR through its C-terminal domain. Recent studies developing antagonists to the AR have concentrated on the C-terminus and specifically: 1) the allosteric pocket and AF-2 activity (Estébanez-Perpiñá *et al* 2007, *PNAS* 104, 16074-16079); 2) *in silico* "drug repurposing" procedure for identification of

nonsteroidal antagonists (Bisson *et al* 2007, *PNAS* 104, 11927 – 11932); and coactivator or corepressor interactions (Chang *et al* 2005, *Mol Endocrinology* 19, 2478-2490; Hur *et al* 2004, *PLoS Biol* 2, E274; Estébanez-Perpiñá *et al* 2005, *JBC* 280, 8060-8068; He *et al* 2004, *Mol Cell* 16, 425-438).

The AR-NTD is also a target for drug development (e.g. WO 2000/001813), since the NTD contains Activation-Function-1 (AF_1) which is the essential region required for 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; 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).

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

Recent advances in the development of compounds that modulate AR include the bis-phenol compounds disclosed in published PCT WO 2010/000066 to the British Columbia Cancer Agency Branch and The University of British Columbia. While such compounds appear promising, there remains a need in the art for additional and/or improved compounds that modulate the AR, and which provide treatment for conditions that benefit from such modulation.

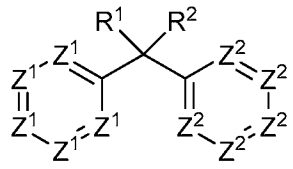
BRIEF SUMMARY

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

nuclear receptors using recombinant proteins, cells maintained in culture, and/or animal models.

This invention is also based in part on the surprising discovery that the compounds described herein, may also be used to modulate AR activity either *in vivo* or *in vitro* for both research and therapeutic uses. The compounds may be used in an effective amount so that androgen receptor activity may be modulated. The AR may be mammalian. Alternatively, the androgen receptor may be human. In particular, the compounds may be used to inhibit the AR. The compounds modulatory activity may be used in either an *in vivo* or an *in vitro* model for the study of at least one of the following indications: prostate cancer, breast cancer, ovarian cancer, salivary gland carcinoma, endometrial cancer, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty (testoxicosis), spinal and bulbar muscular atrophy (SBMA, Kennedy's disease), and age-related macular degeneration. Furthermore, the compounds modulatory activity may be used for the treatment of at least one of the following indications: 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. The indication for treatment may be prostate cancer. The prostate cancer may be castration-resistant prostate cancer. The prostate cancer may be androgen-dependent prostate cancer. In other examples the indication is Kennedy's disease.

In accordance with one embodiment, there is provided a compound having a structure of Formula I:



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or a pharmaceutically acceptable salt or tautomer thereof, wherein Z^1, Z^2 R^1 and R^2 are as defined herein.

In other embodiments, the present disclosure provides the use of a compound of Formula I, for modulating androgen receptor (AR) activity. Methods for modulating AR, as well as pharmaceutical compositions comprising a compound of Formula I and a pharmaceutically acceptable excipient are also provided.

In addition, the present disclosure provides combination therapy treatments for any of the disease states disclosed herein, for example prostate cancer or Kennedy's disease. The disclosed therapies include use of a pharmaceutical composition comprising a compound of Formula I, an additional therapeutic agent and a pharmaceutically acceptable excipient. Methods and compositions related to the same are also provided.

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

DETAILED DESCRIPTION

As used herein, the phrase "C_x-C_y alkyl" is used as it is normally understood to a person of skill in the art and often refers to a chemical entity that has a carbon skeleton or main carbon chain comprising a number from x to y (with all individual integers within the range included, including integers x and y) of carbon atoms. For example a "C_1-C_{10} alkyl" is a chemical entity that has 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atom(s) in its carbon skeleton or main chain. Non-limiting examples of saturated C_1-C_{10} alkyl include methyl, ethyl, n-propyl, i-propyl, sec-propyl, n-butyl, i-butyl, sec-butyl, t-butyl and n-penty, n-hexyl, n-heptane, and the like. Non-limiting examples of C_2-C_{10} alkenyl include vinyl, allyl, isopropenyl, 1-propene-2-yl, 1-butene-1-yl, 1-butene-2-yl, 1-butene-3-yl, 2-butene-1-yl, 2-butene-2-yl, penteneyl , hexeneyl, and the like. Non-limiting examples of C_2-C_{10} alkynyl include ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Unless stated otherwise specifically in the specification, an alkyl group may be optionally substituted (*i.e.*, a hydrogen atom in the alkyl group may be replaced with an optional substituent).

As used herein, the term "cyclic C_x-C_y alkyl" is used as it is normally understood to a person of skill in the art and often refers to a compound or a chemical entity in which at least a portion of the carbon skeleton or main chain of the chemical entity is bonded in such a way so as to form a 'loop', circle or ring of atoms that are bonded together. The atoms do not have to all be directly bonded to each other, but rather may be directly bonded to as few as two other atoms in the 'loop'. Non-limiting

examples of cyclic alkyls include benzene, toluene, cyclopentane, bisphenol and 1-chloro-3-ethylcyclohexane.

As used herein, the term "branched" is used as it is normally understood to a person of skill in the art and often refers to a chemical entity that comprises a skeleton or main chain that splits off into more than one contiguous chain. The portions of the skeleton or main chain that split off in more than one direction may be linear, cyclic or any combination thereof. Non-limiting examples of a branched alkyl are tert-butyl and isopropyl.

As used herein, the term "unbranched" is used as it is normally understood to a person of skill in the art and often refers to a chemical entity that comprises a skeleton or main chain that does not split off into more that one contiguous chain. Non-limiting examples of unbranched alkyls are methyl, ethyl, n-propyl, and n-butyl.

"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 may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems. Aryl radicals include, but are not limited to, aryl radicals derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals that are optionally substituted.

"Aralkyl" refers to a radical of the formula $-R_b-R_c$ where R_b is an alkylene chain as defined above and R_c is one or more aryl radicals as defined above, for example, benzyl, diphenylmethyl and the like. Unless stated otherwise specifically in the specification, an aralkyl group may be optionally substituted.

As used herein, the term "substituted" is used as it is normally understood to a person of skill in the art and often refers to a chemical entity that has one chemical group replaced with a different chemical group that contains one or more heteroatoms. Unless otherwise specified, a substituted alkyl is an alkyl in which one or more hydrogen atom(s) is/are replaced with one or more atom(s) that is/are not hydrogen(s). For example, chloromethyl is a non-limiting example of a substituted

alkyl, more particularly an example of a substituted methyl. Aminoethyl is another non-limiting example of a substituted alkyl, more particularly it is a substituted ethyl.

As used herein, the term "unsubstituted" is used as it is normally understood to a person of skill in the art and often refers to a chemical entity that is a hydrocarbon and/or does not contain a heteroatom. Non-limiting examples of unsubstituted alkyls include methyl, ethyl, tert-butyl, and pentyl.

As used herein, the term "saturated" when referring to a chemical entity is used as it is normally understood to a person of skill in the art and often refers to a chemical entity that comprises only single bonds. Non-limiting examples of saturated chemical entities include ethane, tert-butyl, and $N^{+}H_3$.

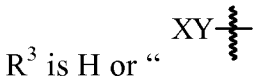
As used herein, C_1-C_{10} alkyl may include, for example, and without limitation, saturated C_1-C_{10} alkyl, C_2-C_{10} alkenyl and C_2-C_{10} alkynyl. Non-limiting examples of saturated C_1-C_{10} alkyl may include methyl, ethyl, n-propyl, i-propyl, sec-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, n-pentyl, i-pentyl, sec-pentyl, t-pentyl, n-hexyl, i-hexyl, 1,2-dimethylpropyl, 2-ethylpropyl, 1-methyl-2-ethylpropyl, 1-ethyl-2-methylpropyl, 1,1,2-trimethylpropyl, 1,1,2-triethylpropyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 2-ethylbutyl, 1,3-dimethylbutyl, 2-methylpentyl, 3-methylpentyl, sec-hexyl, t-hexyl, n-heptyl, i-heptyl, sec-heptyl, t-heptyl, n-octyl, i-octyl, sec-octyl, t-octyl, n-nonyl, i-nonyl, sec-nonyl, t-nonyl, n-decyl, i-decyl, sec-decyl and t-decyl. Non-limiting examples of C_2-C_{10} alkenyl may include vinyl, allyl, isopropenyl, 1-propene-2-yl, 1-butene-1-yl, 1-butene-2-yl, 1-butene-3-yl, 2-butene-1-yl, 2-butene-2-yl, octenyl and decenyl. Non-limiting examples of C_2-C_{10} alkynyl may include ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl and decynyl. Saturated C_1-C_{10} alkyl, C_2-C_{10} alkenyl or C_2-C_{10} alkynyl may be, for example, and without limitation, interrupted by one or more heteroatoms which are independently nitrogen, sulfur or oxygen.

As used herein, cyclic C_3-C_{10} alkyl may include, for example, and without limitation, saturated C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkenyl, C_3-C_{10} cycloalkynyl, $C_{6\text{-}10}$ aryl, $C_{6\text{-}9}$ aryl-$C_{1\text{-}4}$ alkyl, $C_{6\text{-}8}$ aryl-$C_{2\text{-}4}$ alkenyl, $C_{6\text{-}8}$ aryl-$C_{2\text{-}4}$ alkynyl, a 4- to 10-membered non-aromatic heterocyclic group containing one or more heteroatoms which are independently nitrogen, sulfur or oxygen, and a 5- to 10-membered aromatic heterocyclic group containing one or more heteroatoms which are independently nitrogen, sulfur or oxygen. Non-limiting examples of the saturated C_3-

C_{10} cycloalkyl group may include cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, cyclooctanyl, cyclononanyl and cyclodecanyl. Non-limiting examples of the C_3-C_{10} cycloalkenyl group may include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclononanenyl and cyclodecanenyl. Non-limiting examples of the C_6-C_{10} aryl group may include phenyl (Ph), pentalenyl, indenyl, naphthyl, and azulenyl. The C_{6-9} aryl-C_{1-4} alkyl group may be, for example, and without limitation, a C_{1-4} alkyl group as defined anywhere above having a C_{6-9} aryl group as defined anywhere above as a substituent. The C_{6-8} aryl-C_{2-4} alkenyl group may be, for example, and without limitation, a C_{2-4} alkenyl as defined anywhere above having a C_{6-8} aryl group as defined anywhere above as a substituent. The C_{6-8} aryl-C_{2-4} alkynyl group may be, for example, and without limitation, a C_{2-4} alkynyl group as defined anywhere above having a C_{6-8} aryl group as defined anywhere above as a substituent. Non-limiting examples of the 4- to 10-membered non-aromatic heterocyclic group containing one or more heteroatoms which are independently nitrogen, sulfur or oxygen may include pyrrolidinyl, pyrrolinyl, piperidinyl, piperazinyl, imidazolinyl, pyrazolidinyl, imidazolydinyl, morpholinyl, tetrahydropyranyl, azetidinyl, oxetanyl, oxathiolanyl, phthalimide and succinimide. Non-limiting examples of the 5- to 10-membered aromatic heterocyclic group containing one or more heteroatoms which are independently nitrogen, sulfur or oxygen may include pyrrolyl, pyridinyl, pyridazinyl, pyrimidinyl, pirazinyl, imidazolyl, thiazolyl and oxazolyl.

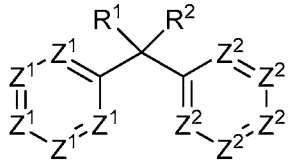
Non-limiting examples of one to ten carbon substituted or unsubstituted acyl include acetyl, propionyl, butanoyl and pentanoyl. Non-limiting examples of C_1-C_{10} alkoxy include methoxy, ethoxy, propoxy and butoxy.

As used herein, the symbol "  " (hereinafter may be referred to as "a point of attachment bond") denotes a bond that is a point of attachment between two chemical entities, one of which is depicted as being attached to the point of attachment bond and the other of which is not depicted as being attached to the point of attachment bond. For example, "  " indicates that the chemical entity "XY" is bonded to another chemical entity via the point of attachment bond. Furthermore, the specific

point of attachment to the non-depicted chemical entity may be specified by inference. For example, the compound CH_3-R^3, wherein R^3 is H or "  " infers that when R^3 is "XY", the point of attachment bond is the same bond as the bond by which R^3 is depicted as being bonded to CH_3.

"Halo" refers to fluoro (F), chloro (Cl), bromo (Br) or iodo (I). Radioisotopes are included witin the definition of halo. Accordingly, compounds comprising fluoro , chloro , bromo or iodo may also comprise radioisotopes of the same.

As noted above, the present disclosure provides a compound having a structure of Formula I:



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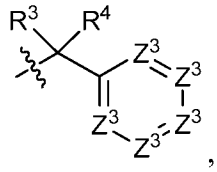
or a pharmaceutically acceptable salt or tautomer thereof, wherein:

at least one Z^1 is independently C-Q;

at least one Z^2 is independently C-W, wherein W is



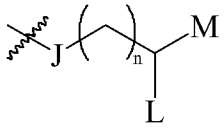
,

at least one Z^3 is independently C-T, CH, CCH_3, CF, CCl, CBr, CI, COH, CG^1, COG^1, CNH_2, $CNHG^1$, $CNG^1{}_2$, $COSO_3H$, $COPO_3H_2$, CSG^1, $CSOG^1$, or CSO_2G^1,

each remaining Z^1, Z^2 and Z^3 is, at each occurrence, independently C-T, N, CH, CCH_3, CF, CCl, CBr, CI, COH, CG^1, COG^1, CNH_2, $CNHG^1$, $CNG^1{}_2$, $COSO_3H$, $COPO_3H_2$, CSG^1, $CSOG^1$, or CSO_2G^1;

R^1, R^2, R^3 and R^4 are each independently H or a linear or branched, substituted or unsubstituted, saturated or unsaturated C_1-C_{10} alkyl, or R^1 and R^2, or R^3 and R^4 may independently together form a substituted or unsubstituted, saturated or unsaturated cyclic C_3-C_{10} alkyl or R^1 and R^2, or R^3 and R^4 may independently together

form =CR″R‴, wherein R″ and R‴ are each independently a linear or branched, substituted or unsubstituted, saturated or unsaturated C_1-C_{10} alkyl, aryl or aralkyl;

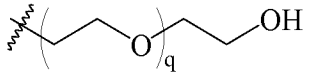
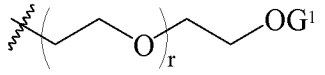
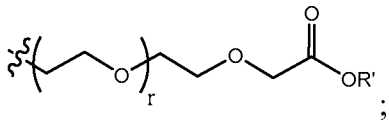
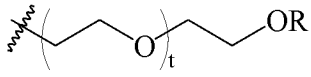
Q is  ;

J is G^1, O, CH_2, CHG^1, $CG^1{}_2$, S, NH, NG^1, SO, SO_2, or NR;

M is H, F, Cl, Br, CH_2OH, CH_2OD, CH_2OG^1, CH_2F, CH_2Cl, $CHCl_2$, CCl_3, CH_2Br, $CHBr_2$, CBr_3 or C≡CH;

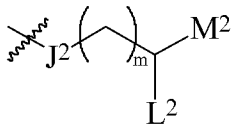
L is H or A-D;

A is O, S, NH, NG^1, N^+H_2 or N^+HG^1;

D is, at each occurrence, independently H, G^1, R,  ,  ,  ;  or a moiety from TABLE 1;

each of q, r and t may independently be 0, 1, 2, 3, 4, 5, 6 or 7;

n is 0, 1, 2, 3, 4, 5, 6, 7 or 8;

T is, at each occurrence, independently  ;

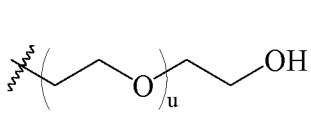
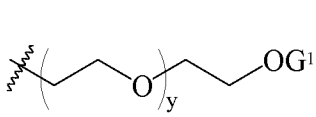
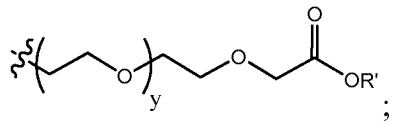
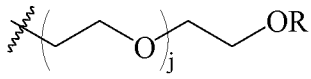
J^2 is, at each occurrence, independently G^1, O, CH_2, CHG^1, $C(G^1)_2$, S, NH, NG^1, SO, SO_2, or NR;

M^2 is, at each occurrence, independently H, CH_3, F, Cl, Br, CH_2F , CH_2Cl, $CHCl_2$, CCl_3, CH_2Br, $CHBr_2$, CBr_3, CH_2OH, CH_2OD^2, CH_2OJ'', G^1, CH_2OG^1, CH_2OR, $CH_2OG^1OG^{1\prime}$, $G^1OG^{1\prime}$, $G^1OG^{1\prime}OG^{1\prime\prime}$, CH_2SG^1, CH_2NH_2, CH_2NHG^1, $CH_2NG^1{}_2$, or C≡CH;

L^2 is, at each occurrence, independently H or A^2-D^2;

A^2 is, at each occurrence, independently O, S, SO, SO2, NH, NG^1, N^+H_2, or N^+HG^1;

D^2 is, at each occurrence, independently H, G^1, R,

or a moiety selected from TABLE 1;

each of u, y and j are, at each occurrence, independently 0, 1, 2, 3, 4, 5, 6 or 7;

m is, at each occurrence, independently 0, 1, 2, 3, 4, 5, 6, 7 or 8;

J″ and J‴ are, at each occurrence, independently a moiety selected from TABLE 1;

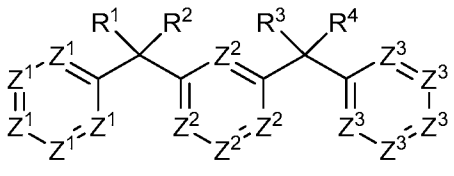
G^1, $G^{1\prime}$ and $G^{1\prime\prime}$ are, at each occurrence, independently a linear or branched, aromatic cyclic or non-aromatic cyclic, substituted or unsubstituted, saturated or unsaturated C_1-C_{10} alkyl, wherein the optional substituents for the C_1-C_{10} alkyl are oxo, CH_2CO_2R', OJ‴, COOH, R^1, OH, OR^1, F, Cl, Br, I, NH_2, NHR^1, $N(R^1)_2$, CN, SH, SR^1, SO_3H, SO_3R^1, SO_2R^1, OSO_3R^1, OR^2, CO_2R^1, $CONH_2$, $CONHR^1$, $CONHR^2$, $CON(R^1)_2$, NHR^2, OPO_3H_3, $CONR^1R^2$, NR^1R^2 or NO_2;

each R' is independently H, linear or branched, aromatic cyclic or non-aromatic cyclic, substituted or unsubstituted, saturated or unsaturated C_1-C_{10} alkyl or a metal counter ion, wherein the metal counter ion is Li, Na, K, Mg or Ca;

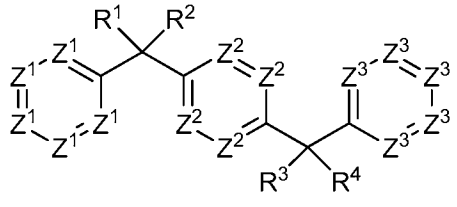
each R^1 is independently unsubstituted C_1-C_{10} alkyl; and

each R and R^2 are independently C_1-C_{10} acyl. For example, in some embodiments at least one Z^3 is independently C-T.

In other embodiments, the compound has a structure of Formula II or III:

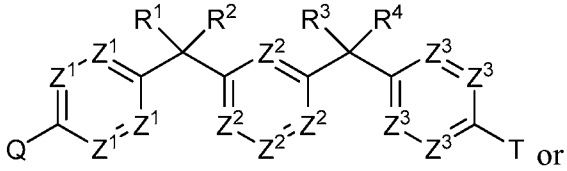

II

or

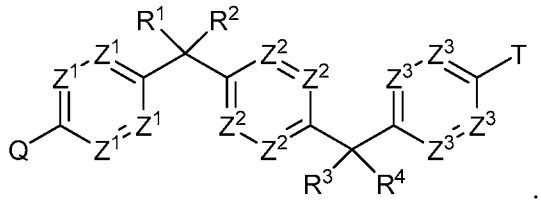

III

.

In some other examples, the compound has a structure of Formula IV or V:

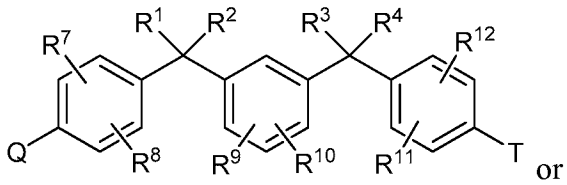


IV

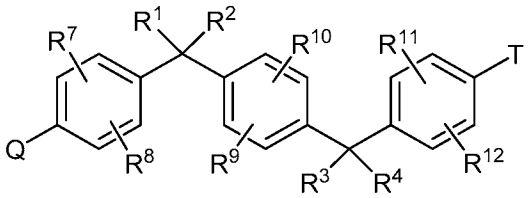


V

In yet other embodiments, the compound has a structure of Formula VI or VII:



VI

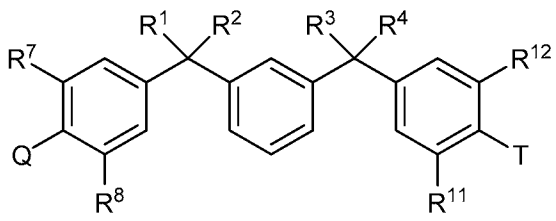


VII

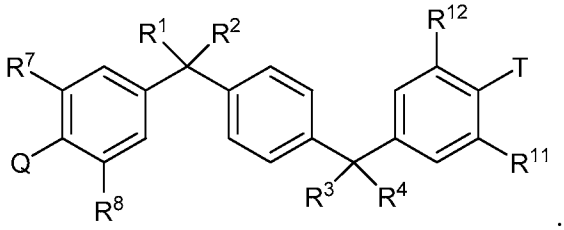
wherein:

R^7, R^8, R^9, R^{10}. R^{11} and R^{12} are each independently hydrogen, halo, or linear or branched, substituted or unsubstituted, saturated or unsaturated C_1-C_{10} alkyl.

In still other embodiments, the compound has a structure of Formula VIII or IX:

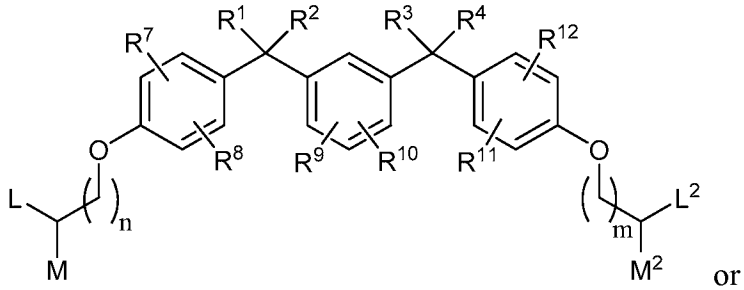


VIII

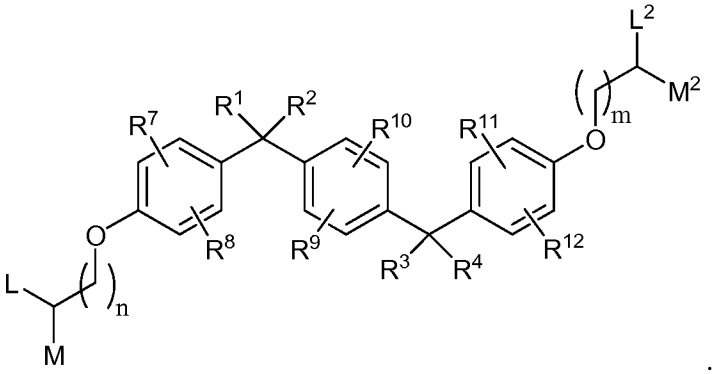


IX

In yet other embodiments, the compound has a structure of Formula X or XI:

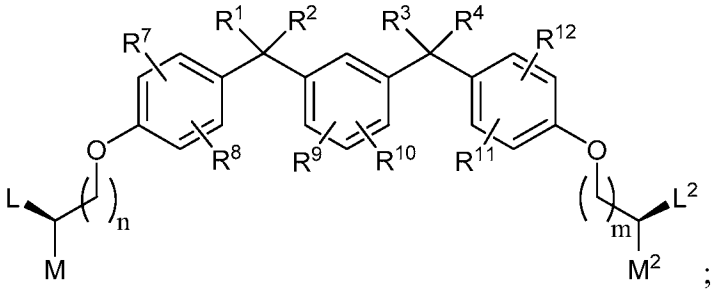


X

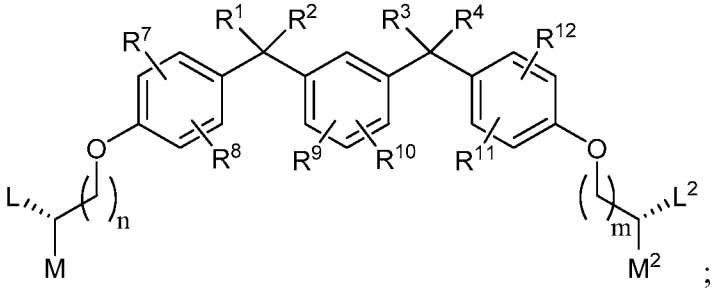


XI

For example in some embodiments, the compound has a structure of Formula Xa, Xb, Xc, Xd, XIa, XIb, XIc or XId:

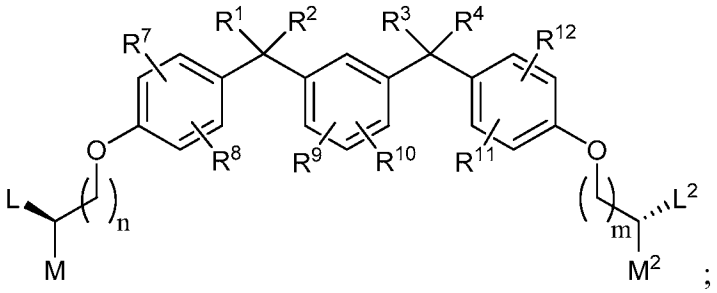


Xa



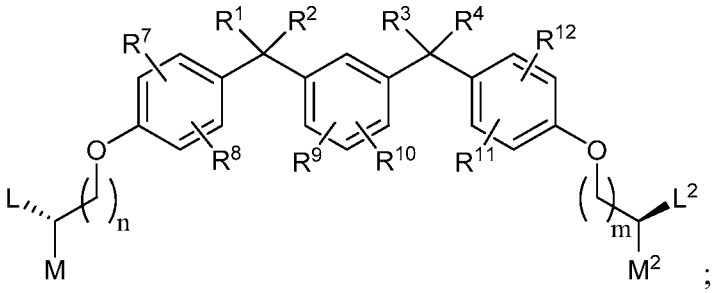
;

Xb



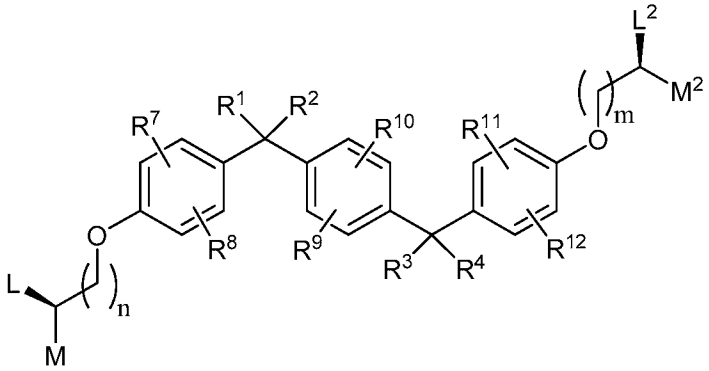
;

Xc



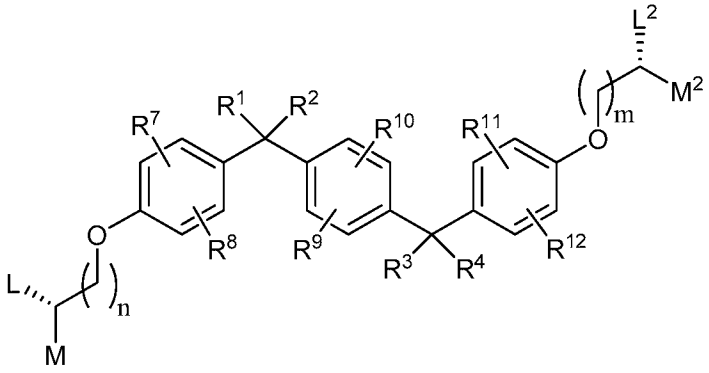
;

Xd



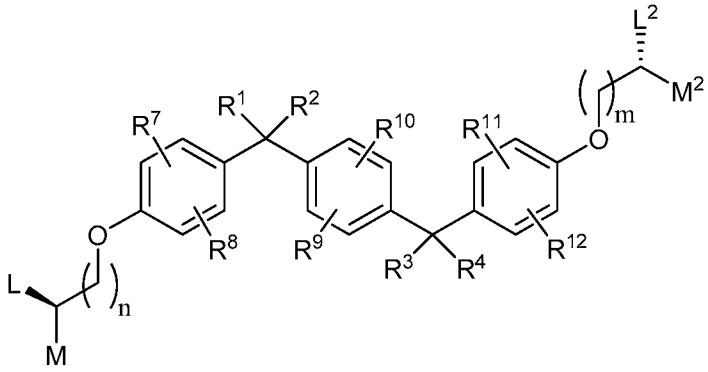
;

XIa



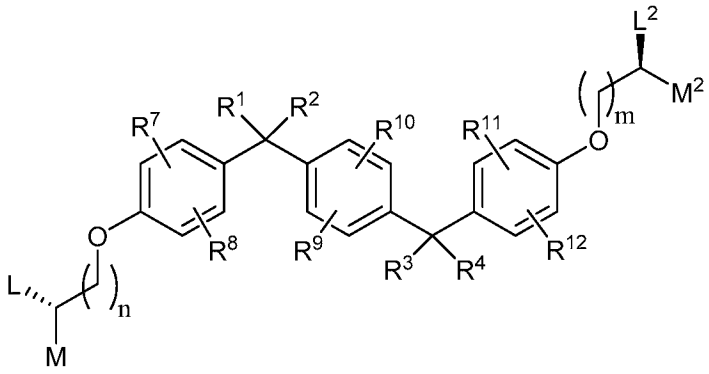
;

XIb



; or

XIc



.

XId

In certain embodiments of any of the foregoing, R^1, R^2, R^3 and R^4 are each independently H or a linear or branched, substituted or unsubstituted, saturated or unsaturated C_1-C_{10} alkyl, or R^1 and R^2, or R^3 and R^4 may independently together form a substituted or unsubstituted, saturated or unsaturated cyclic C_3-C_{10} alkyl.

In certain embodiments of any of the foregoing, R^1, R^2, R^3 and R^4 are each independently H or a linear or branched, substituted or unsubstituted, saturated or unsaturated C_1-C_{10} alkyl. In other embodiments, R^1 and R^2, or R^3 and R^4 may

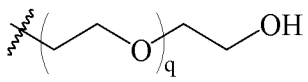
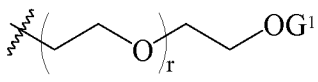
independently together form a substituted or unsubstituted, saturated or unsaturated cyclic C_3-C_{10} alkyl.

In other embodiments, R^1 and R^2, or R^3 and R^4 may independently together form an alkene goup, which is represented herein by the following structure:

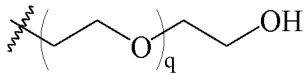
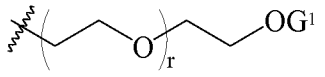
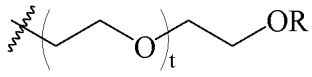
$$=CR''R'''$$

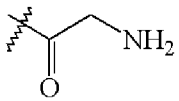
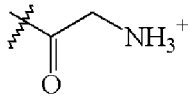
wherein R″ and R‴ are each independently a linear or branched, substituted or unsubstituted, saturated or unsaturated C_1-C_{10} alkyl, aryl or aralkyl.

In other embodiments of the foregoing compound, J is G^1, O, CH_2, CHG^1, $CG^1{}_2$, NH, SO, or NR. For example in some embodiments, J is O.

In other embodiments, M is Cl, Br, CH_2OH, CH_2OD, CH_2OG^1, CH_2F, CH_2Cl, $CHCl_2$, CCl_3, CH_2Br, $CHBr_2$, CBr_3, or C≡CH. In still other embodiments, M is CH_2OH, CH_2F, C≡CH, $CH_2OCH_2C{\equiv}CH$, CH_2O-*n*-butyl, or CH_2OD, wherein D is  or  . For example in some embodiments, M is CH_2OH, and in other embodiments, M is H.

In other embodiments, L is H, and in other embodiments, L is A-D.

In yet other embodiments, A is O while in other embodiments D is H, R,  ,  ,  , or a moiety from TABLE 1; and each of q, r and t is independently 0, 1, 2, 3, 4, 5, 6 or 7. For example in some embodiments, D is H, and in other embodiments D is R.

In certain embodiments, D is a moiety selected from TABLE 1. For example in some embodiments, the moiety from TABLE 1 is  or  .

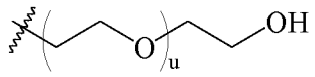
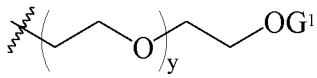
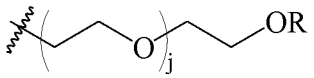
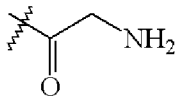
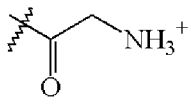
In other embodiments, n is 0, and in some other embodiments n is 1, 2, 3, 4, or 5. For example in some embodiments, n is 1.

In certain embodiments, J^2 is G^1, O, CH_2, CHG^1, $CG^1{}_2$, NH, SO, or NR. For example in some embodiments, J^2 is O.

In other embodiments, M^2 is H, CH_2F, CH_2Cl, CH_2Br, CH_2OH, CH_2OJ'', CH_2OG^1, or C≡CH. For example in some embodiments, M^2 is CH_2F. In other

embodiments, M^2 is CH_2Cl. In still other embodiments, M^2 is CH_2Br. In yet other embodiments, M^2 is CH_2OH, and in some embodiments M^2 is H. In other embodiments, M^2 is C≡CH.

In still other embodiments, L^2 is H, and in other examples L^2 is A^2-D^2.

In certain embodiments, A^2 is O, and in other certain embodiments D^2 is H, R,  ,  ,  , or a moiety from TABLE 1; and each of u, y and j is independently 0, 1, 2, 3, 4, 5, 6 or 7. For example, in some embodiments D^2 is H, and in other embodiments D^2 is R. In still other embodiments, D^2 is a moiety from TABLE 1. For example in some embodiments, the moiety from TABLE 1 is  or  .

In other embodiments of the foregoing compound, m is 0. In still other embodiments, m is 1, 2, 3, 4, or 5. For example in some embodiments, m is 1.

In other examples, M is CH_2OH and L is OH. In still other examples, M^2 is CH_2Cl and L is OH. In even further examples, M is CH_2OH, M^2 is CH_2Cl, L is OH and L^2 is OH. In even further examples, M is CH_2F, M^2 is CH_2Cl, L is OH and L^2 is OH.

In other embodiments, n and m are each 1.

In still other embodiments, at least one of R^1, R^2, R^3 or R^4 is methyl. For example in some embodiments, each of R^1, R^2, R^3 and R^4 is methyl.

In other embodiments, at least one of R^1, R^2, R^3 or R^4 is hydrogen. For example in some embodiments, each of R^1, R^2, R^3 and R^4 is hydrogen.

In other examples, R^1 and R^2 or R^3 and R^4 join to form substituted or unsubstituted cyclohexyl. For example in some embodiments, each of R^1 and R^2 and R^3 and R^4 join to form substituted or unsubstituted cyclohexyl.

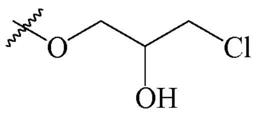
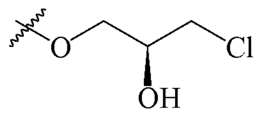
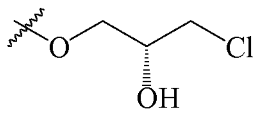
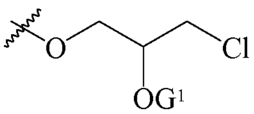
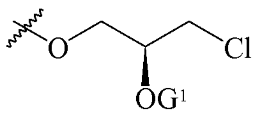
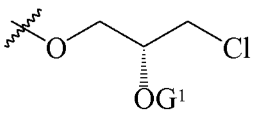
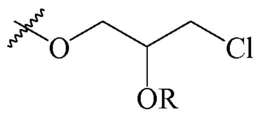
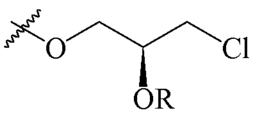
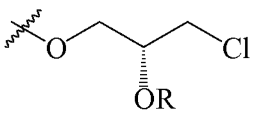
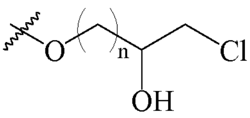
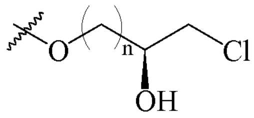
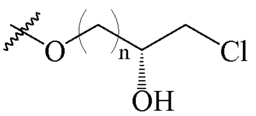
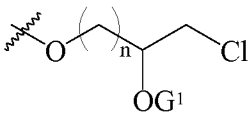
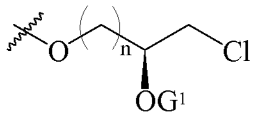
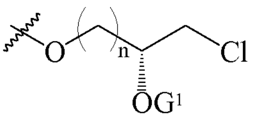
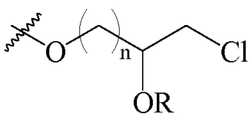
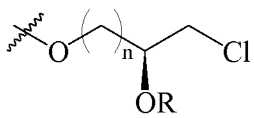
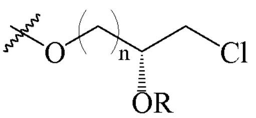
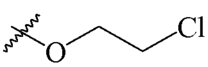
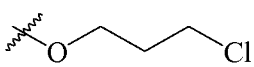
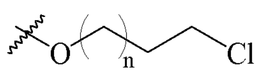
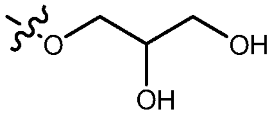
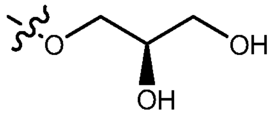
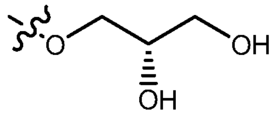
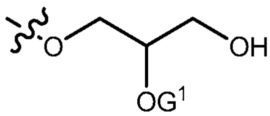
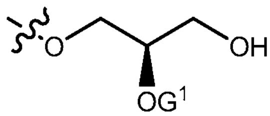
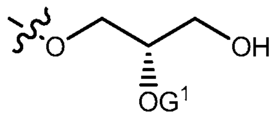
In still other embodiments, at least one of R^7, R^8, R^9, R^{10}, R^{11} or R^{12} is hydrogen. For example in some embodiments, each of R^7, R^8, R^9, R^{10}, R^{11} and R^{12} are hydrogen.

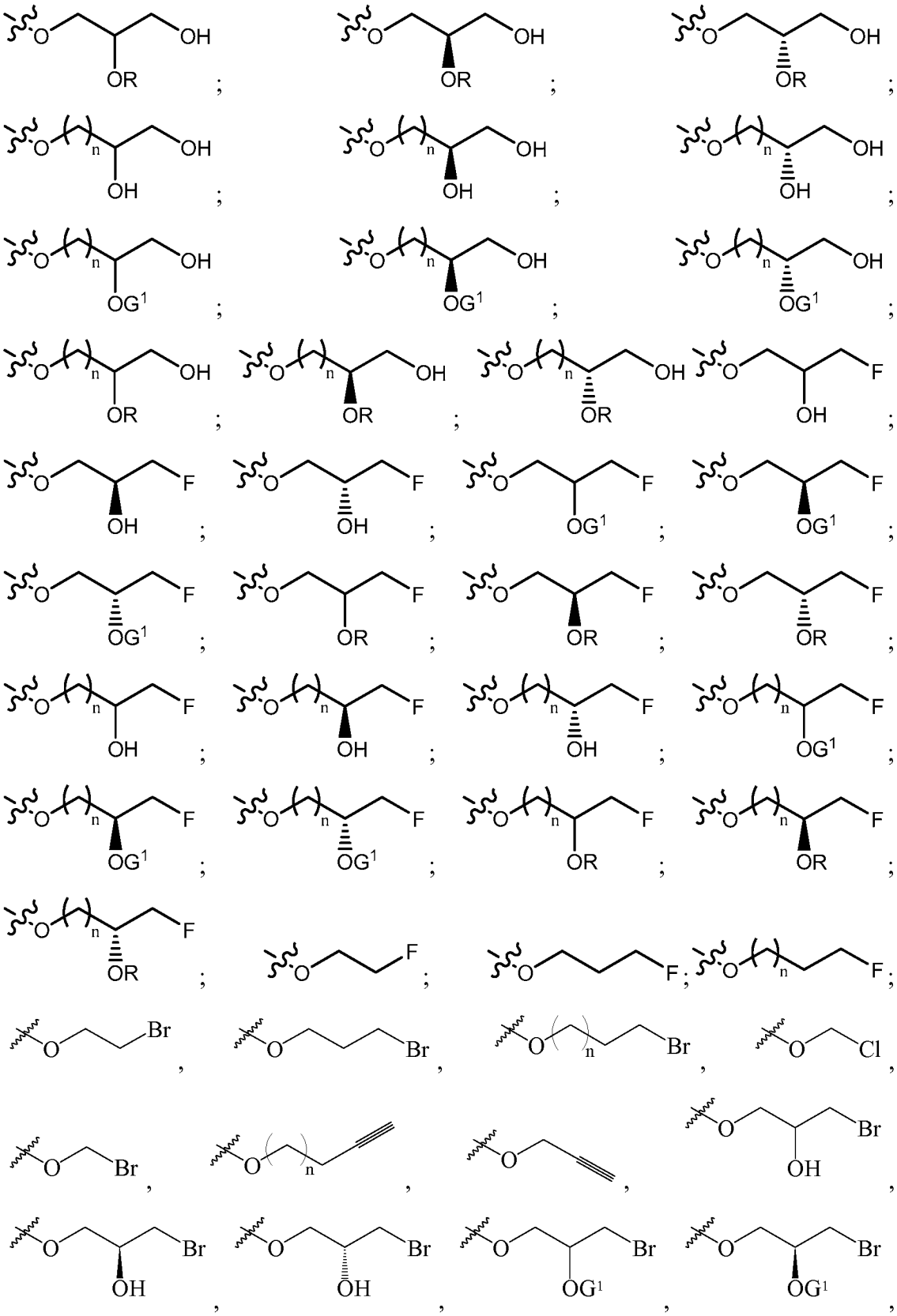
In certain other embodiments,at least one of R^7, R^8, R^9, R^{10}, R^{11} or R^{12} is methyl. For example, each of R^7, R^8, R^9, R^{10}, R^{11} and R^{12} are methyl in some embodiments. In other embodiments, each of R^7, R^8, R^9, and R^{12} are methyl.

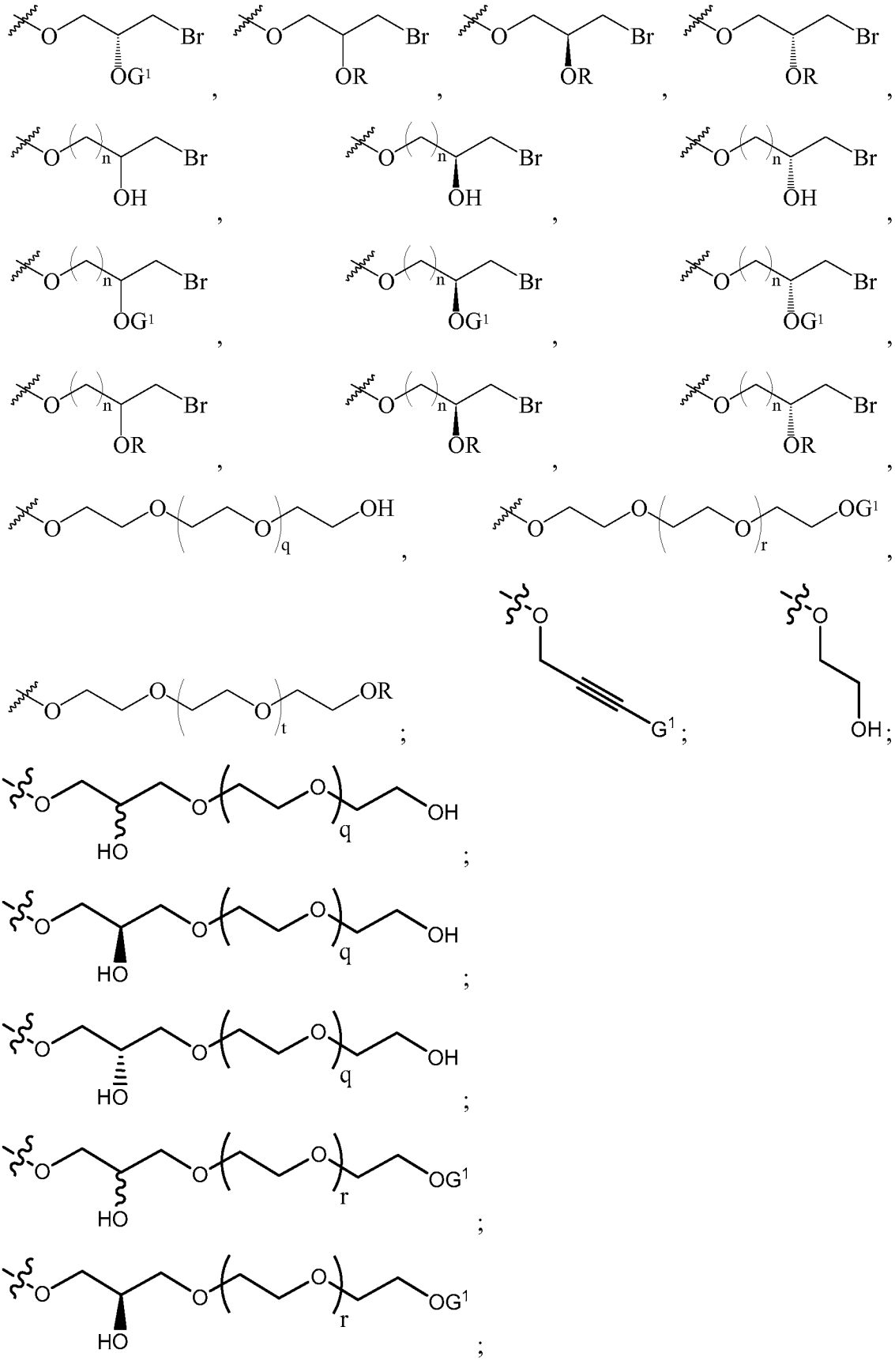
In still other embodiments, at least one of R^7, R^8, R^9, R^{10}, R^{11} or R^{12} is fluoro. For example in some embodiments, each of R^7, R^8, R^9, R^{10}, R^{11} and R^{12} are fluoro. In certain futher embodiments, each of R^7, R^8, R^9, and R^{12} are fluoro.

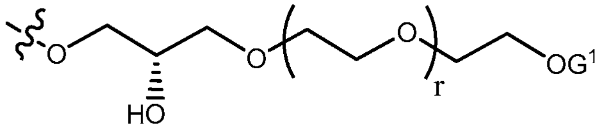
In other aspects, at least one of R^7, R^8, R^9, R^{10}, R^{11} or R^{12} is chloro. For example in some embodiments, each of R^7, R^8, R^9, R^{10}, R^{11} and R^{12} are chloro, while in other examples each of R^7, R^8, R^9, and R^{12} are chloro.

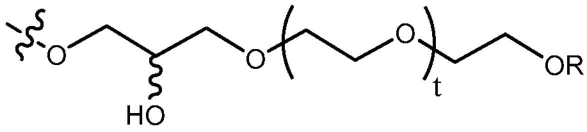
In other embodiments, at least one of R^7, R^8, R^9, R^{10}, R^{11} or R^{12} is bromo. For example in some embodiments, each of R^7, R^8, R^9, R^{10}, R^{11} and R^{12} are bromo, and in other embodiments each of R^7, R^8, R^9, and R^{12} are bromo.

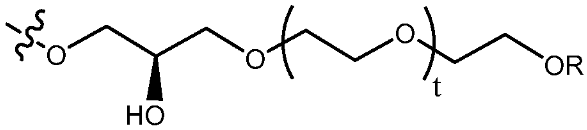
In other embodiments of the foregoing compound, Q is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ;  ;  ;  ;  ;  ;

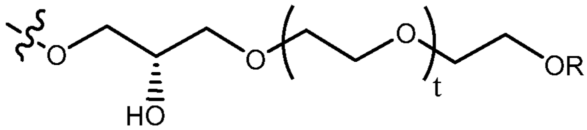
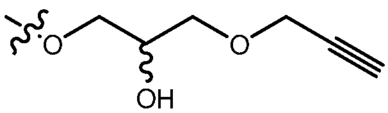


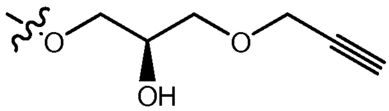
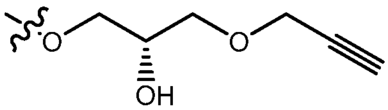


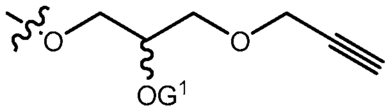
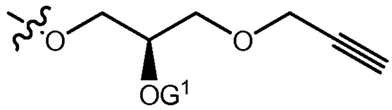
 ;

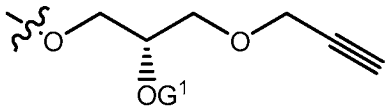
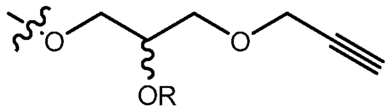
 ;

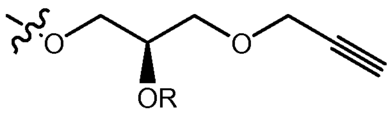
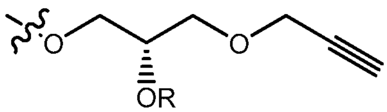
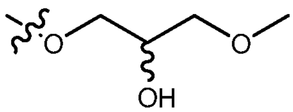
 ;

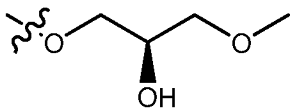
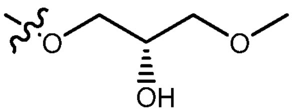
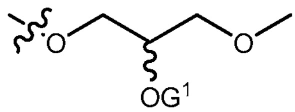
 ;  ;

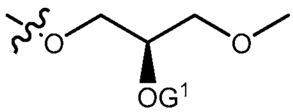
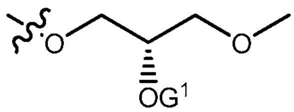
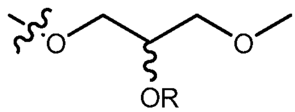
 ;  ;

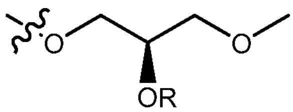
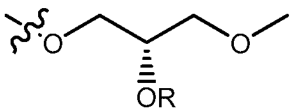
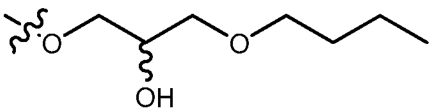
 ;  ;

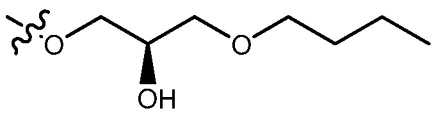
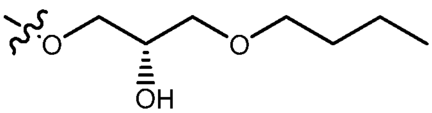
 ;  ;

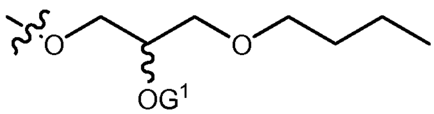
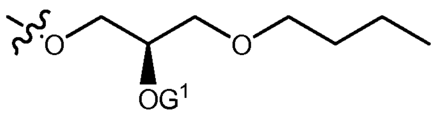
 ;   ;

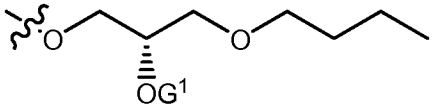
 ;  ;  ;

 ;  ;  ;

 ;  ;  ;

 ;  ;

 ;  ;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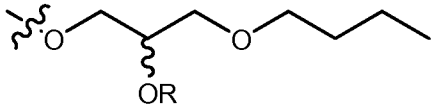
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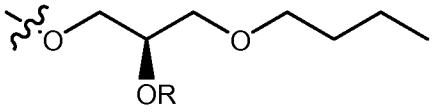
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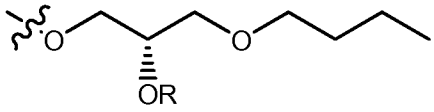
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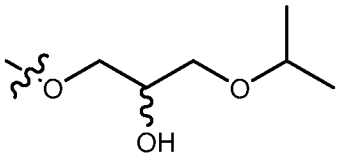
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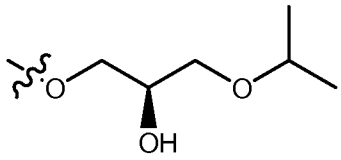
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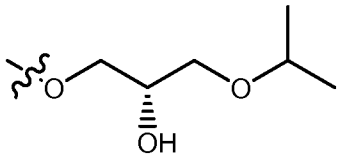
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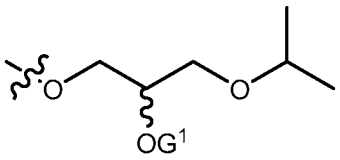
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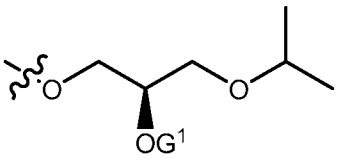
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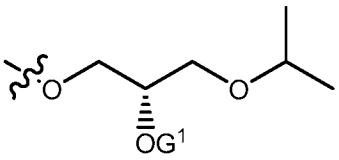
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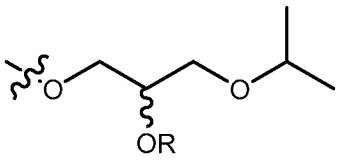
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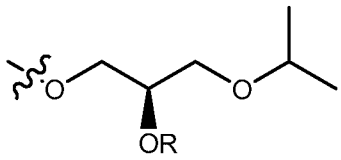
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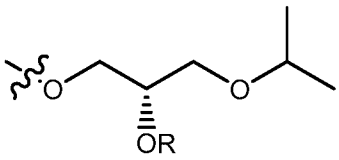
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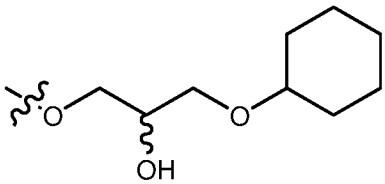
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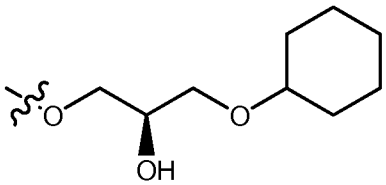
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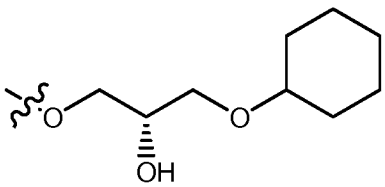
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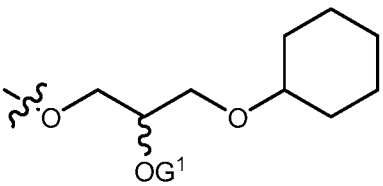
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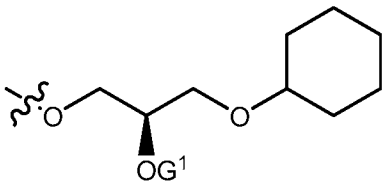
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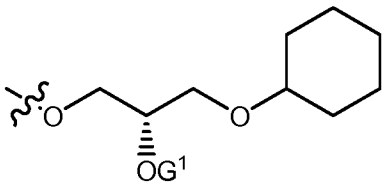
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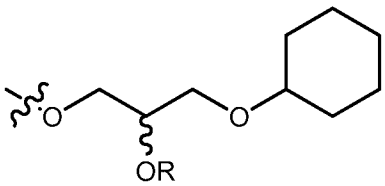
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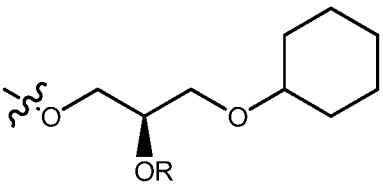
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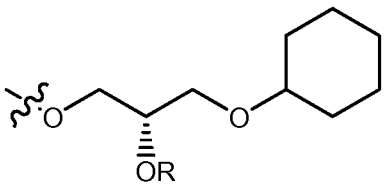
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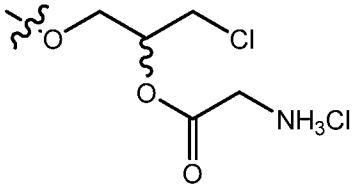
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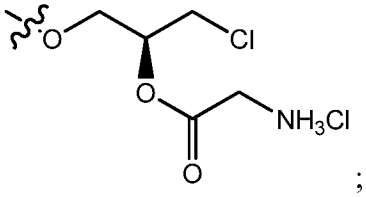
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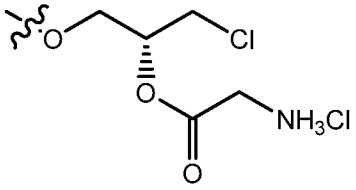
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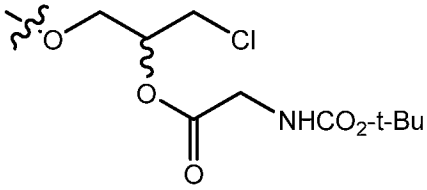
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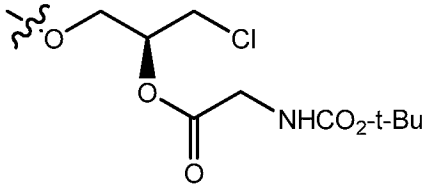
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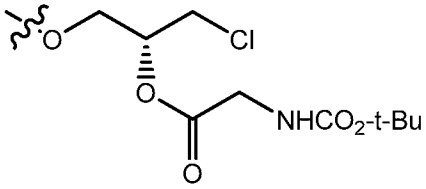
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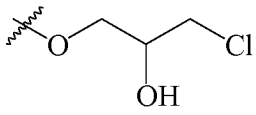
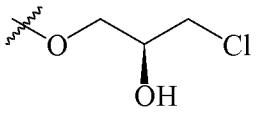
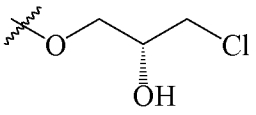
T is 
, 
, 
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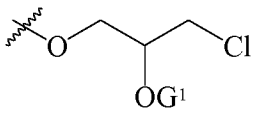
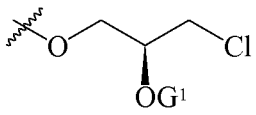
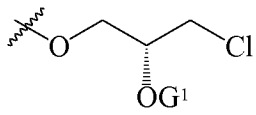
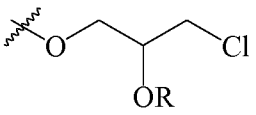

, 
, 
, 
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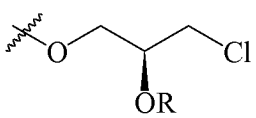
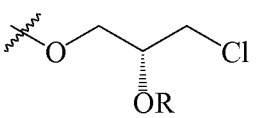
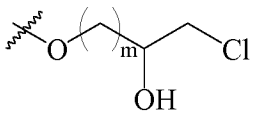
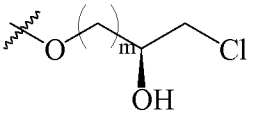

, 
, 
, 
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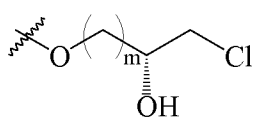
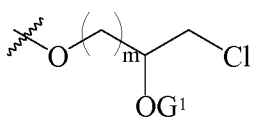
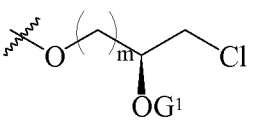

, 
, 
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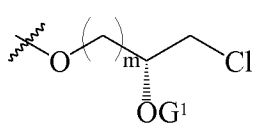
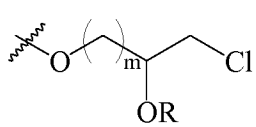
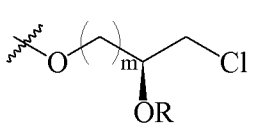

, 
, 
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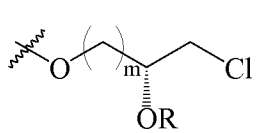
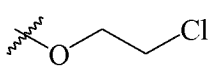
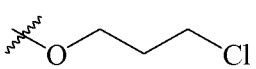
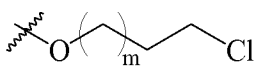

, 
, 
, 
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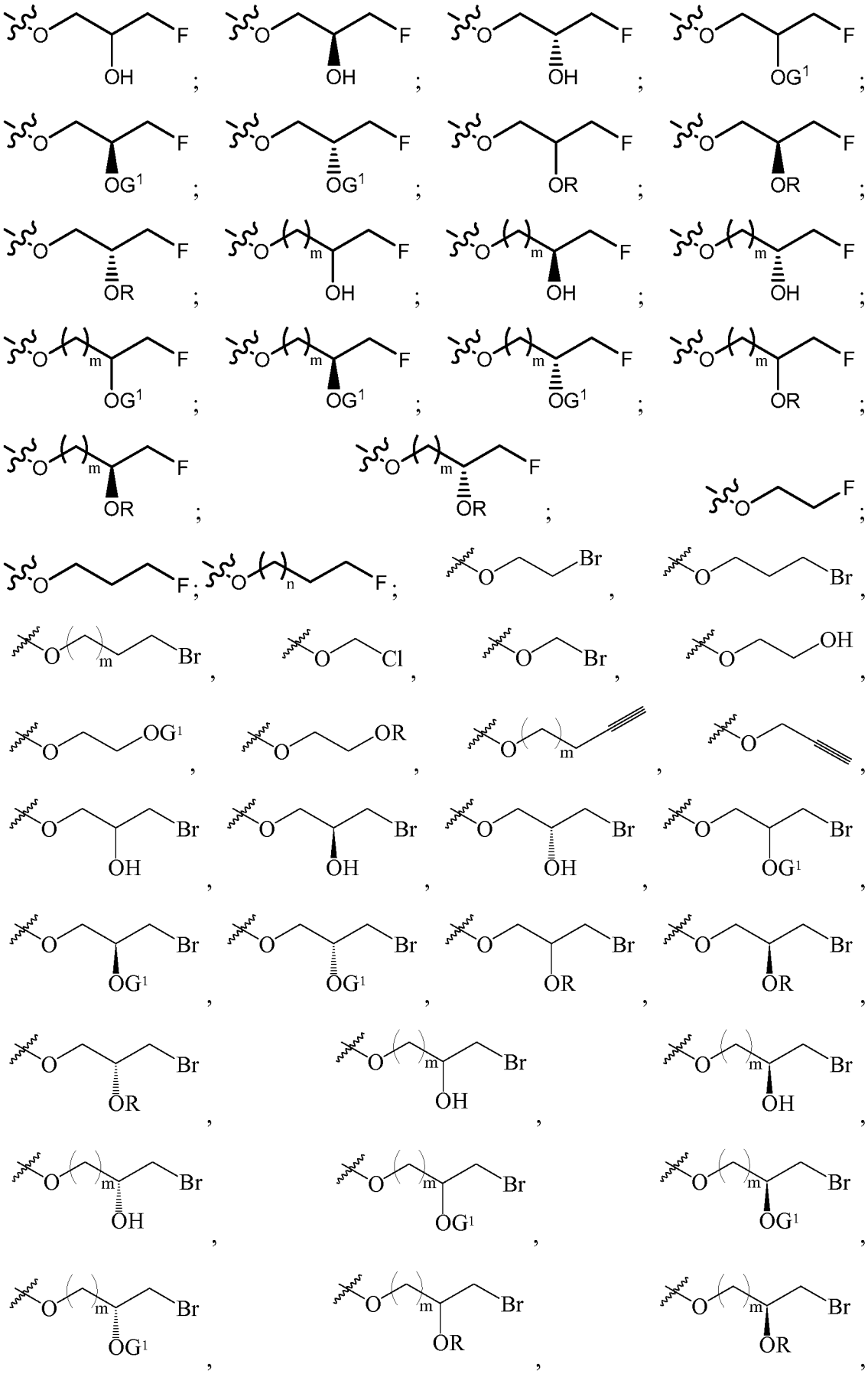

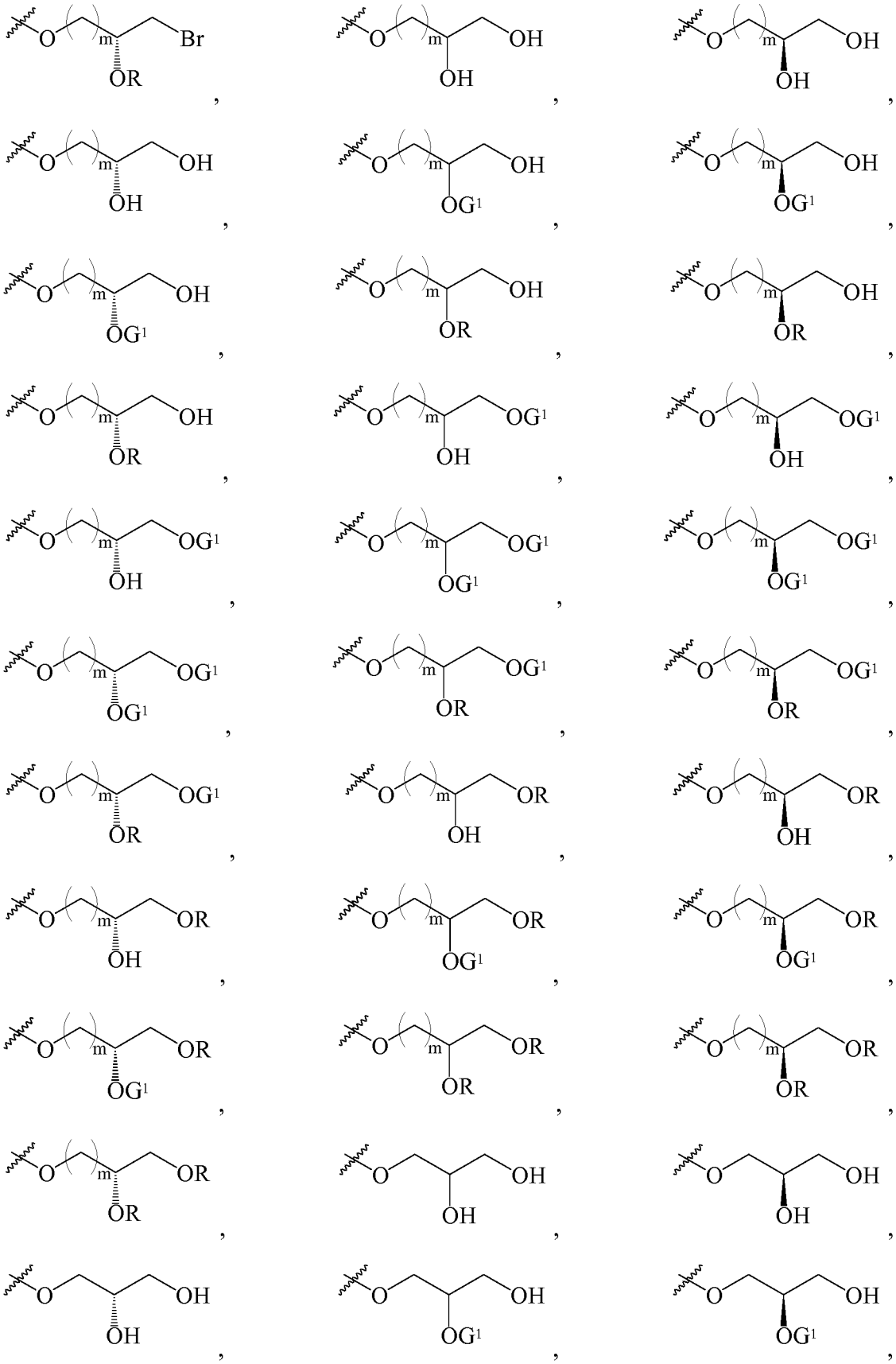

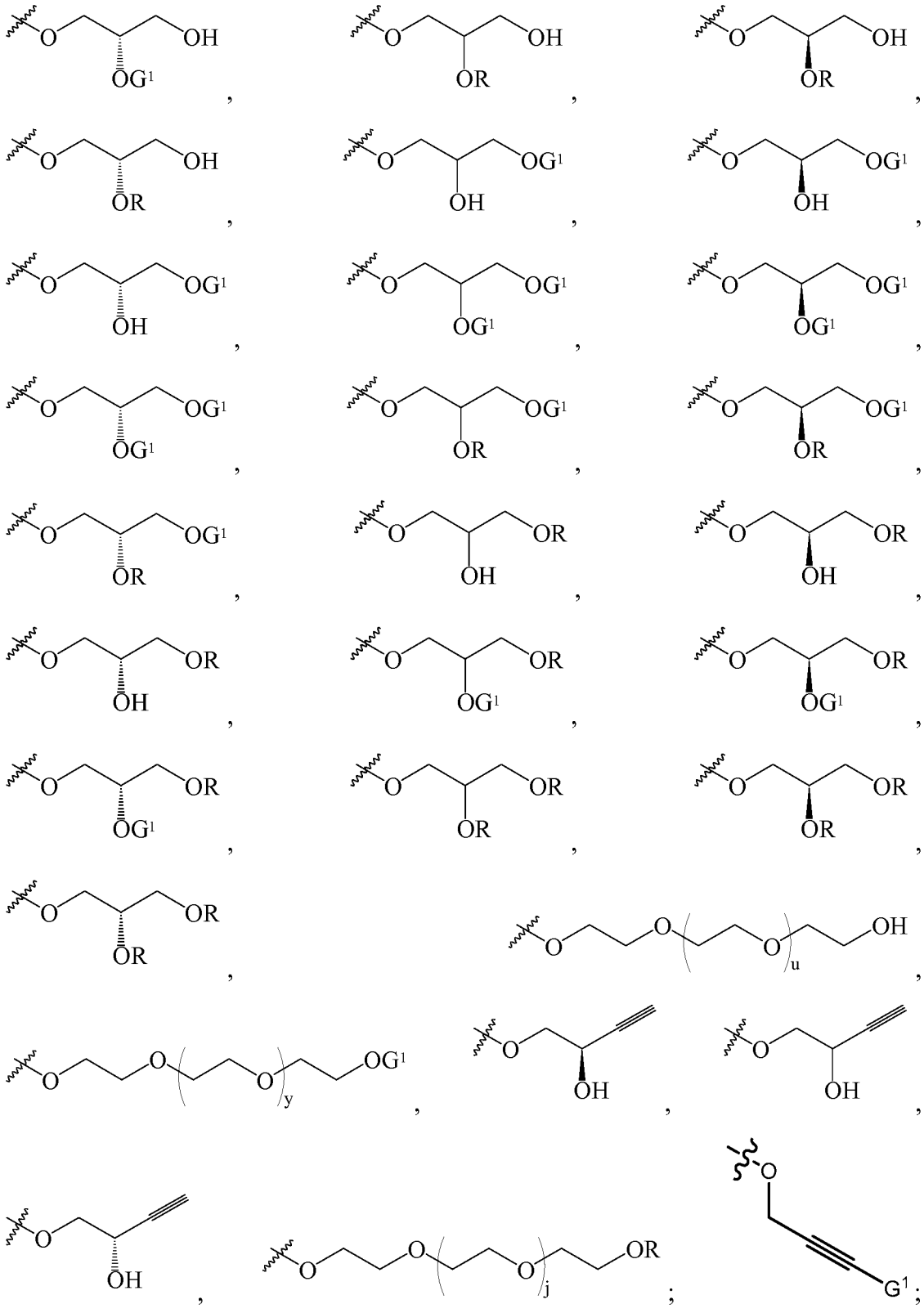

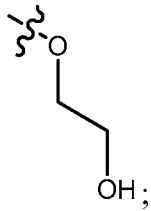
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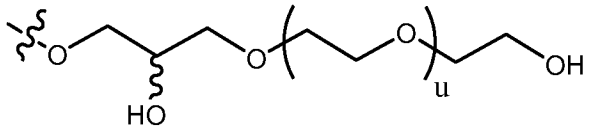
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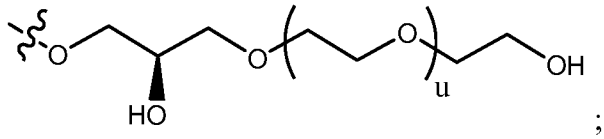
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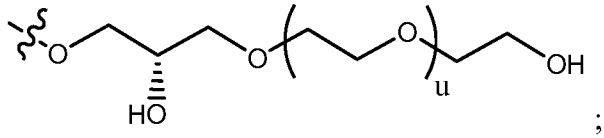
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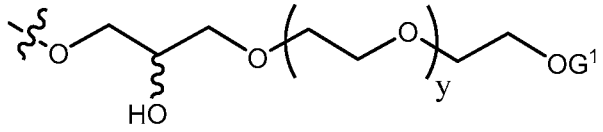
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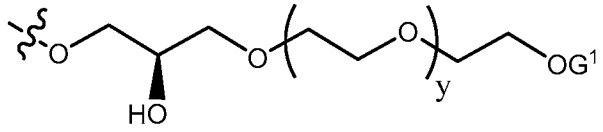
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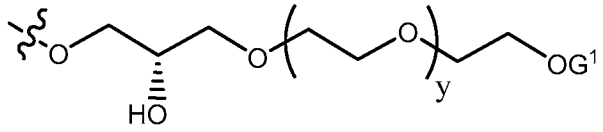
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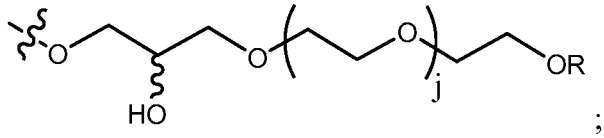
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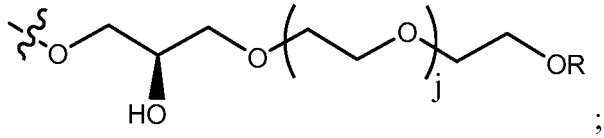
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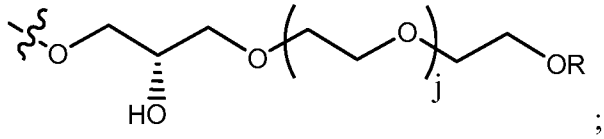
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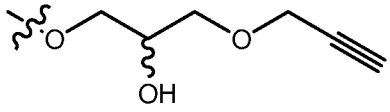
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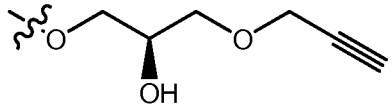
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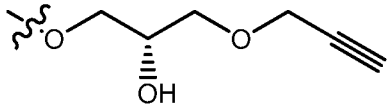
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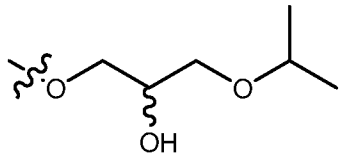
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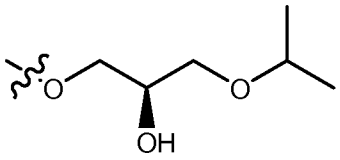
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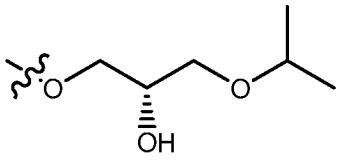
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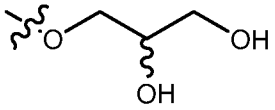
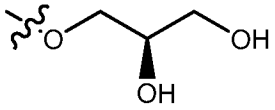
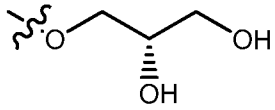
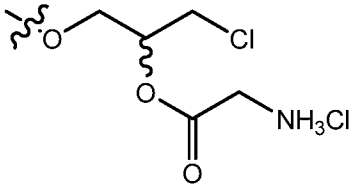
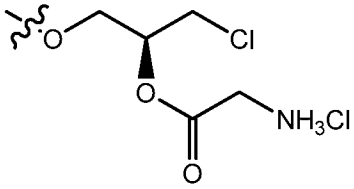
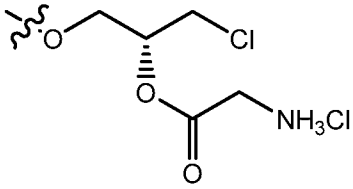
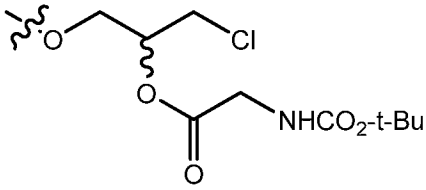
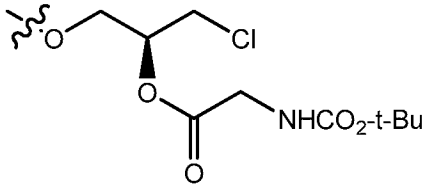
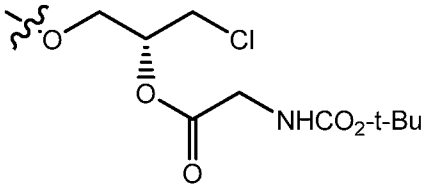
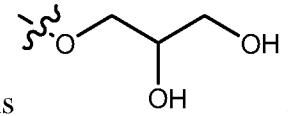
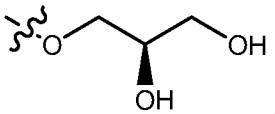
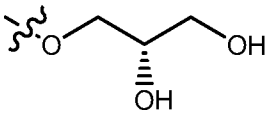
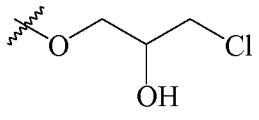
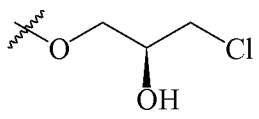
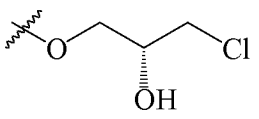
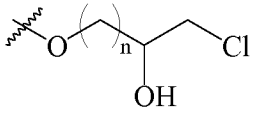
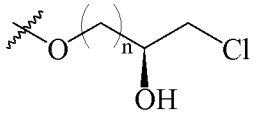
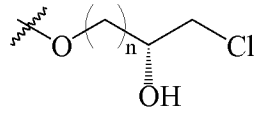
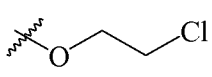
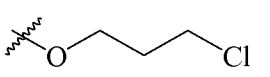
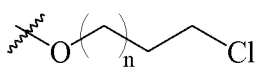
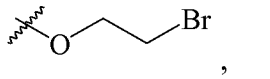
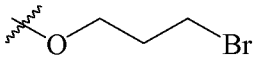
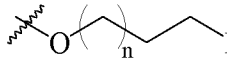
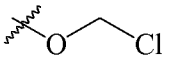
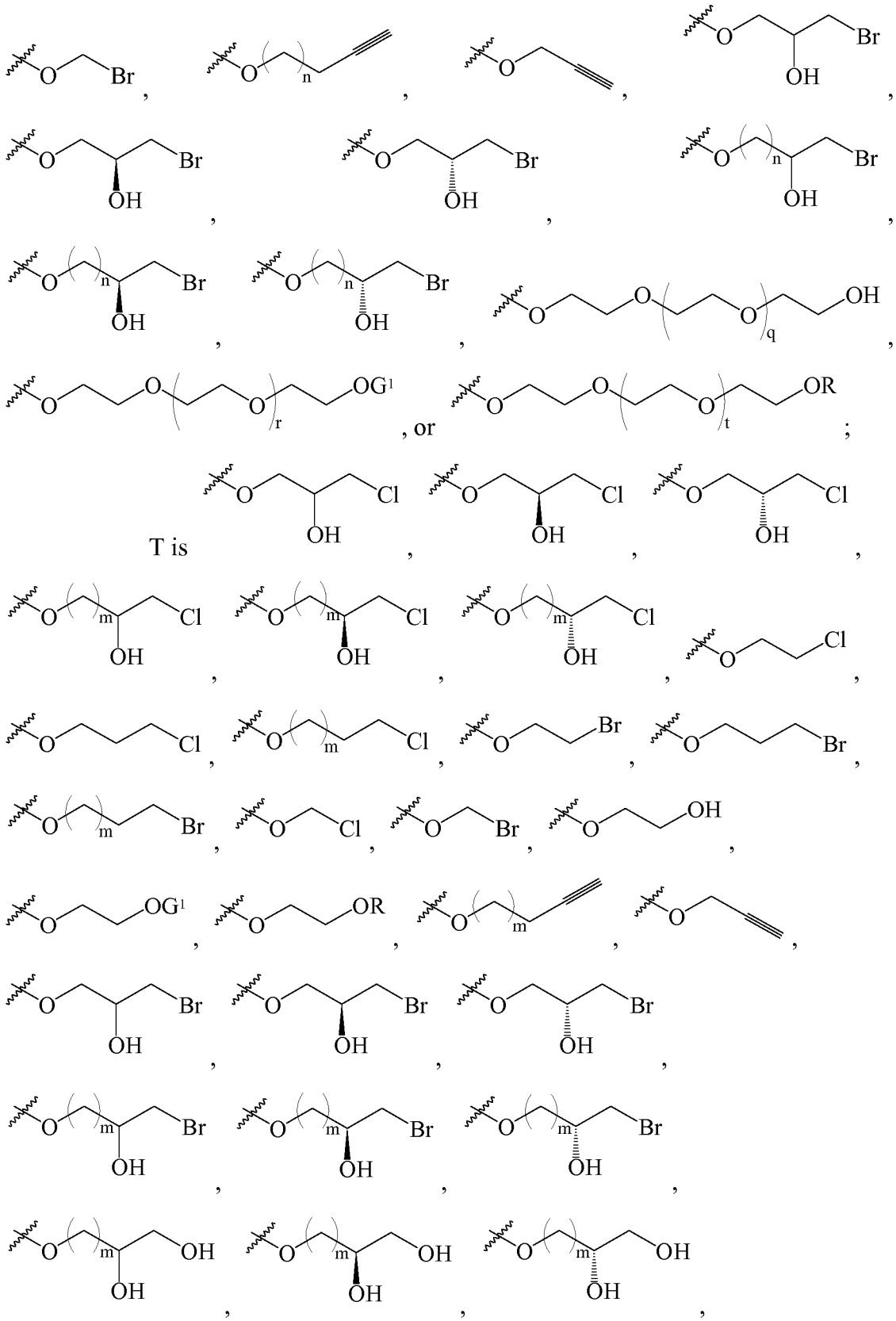










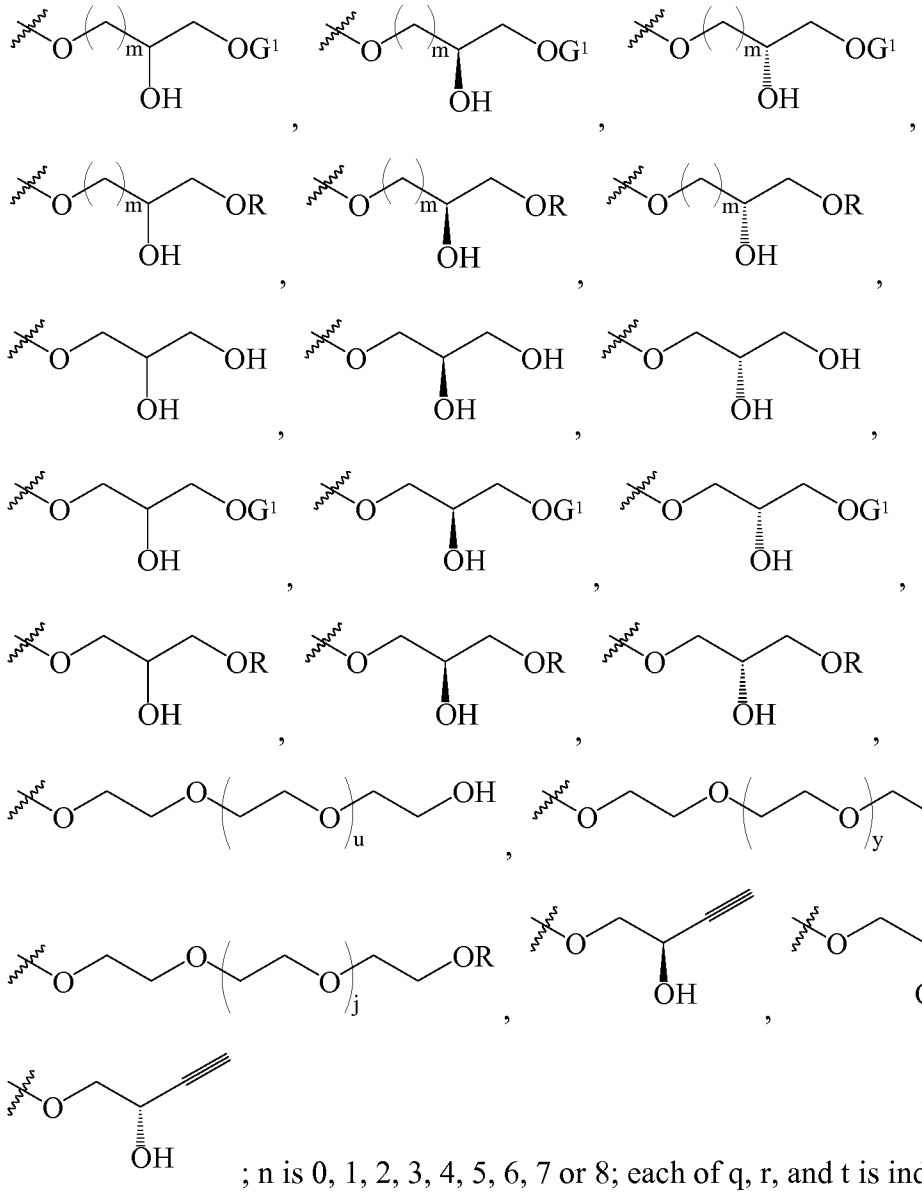
; n is 0, 1, 2, 3, 4, 5, 6, 7 or 8; each of q, r, and t is independently 0, 1, 2, 3, 4, 5, 6 or 7; m is 0, 1, 2, 3, 4, 5, 6, 7 or 8; each of u, j and y is independently 0, 1, 2, 3, 4, 5, 6 or 7 and each G^1 is independently linear or branched, substituted or unsubstituted, saturated or unsaturated C_1-C_{10} alkyl, wherein the optional substituents are selected from oxo, OJ′″, COOH, OH, F, Cl, Br, I, NH_2, CN, SH, SO_3H, $CONH_2$, OPO_3H_3 and NO_2.

In still other embodiments, Q is  ;

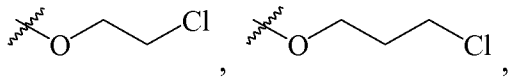


 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,

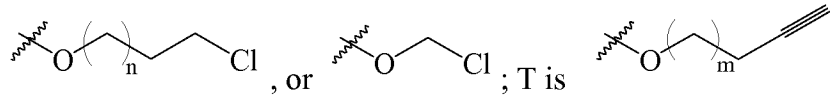


T is

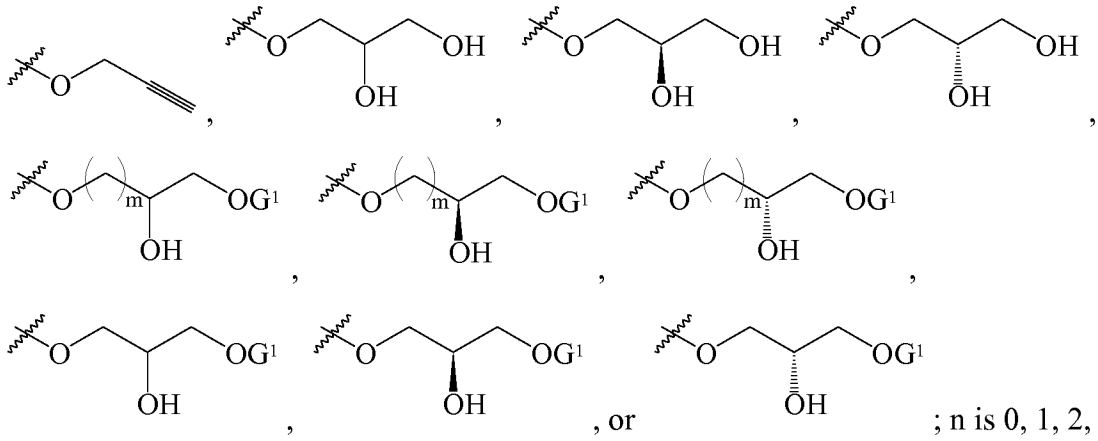


; n is 0, 1, 2, 3, 4, 5, 6, 7 or 8; each of q, r, and t is independently 0, 1, 2, 3, 4, 5, 6 or 7; m is 0, 1, 2, 3, 4, 5, 6, 7 or 8; each of u, j and y is independently 0, 1, 2, 3, 4, 5, 6 or 7 and each G^1 is independently linear or branched, substituted or unsubstituted, saturated or unsaturated C_1-C_{10} alkyl, wherein the optional substituents are selected from oxo, OJ′″, COOH, OH, F, Cl, Br, I, NH_2, CN, SH, SO_3H, $CONH_2$, OPO_3H_3, and NO_2.

In other embodiments, Q is 

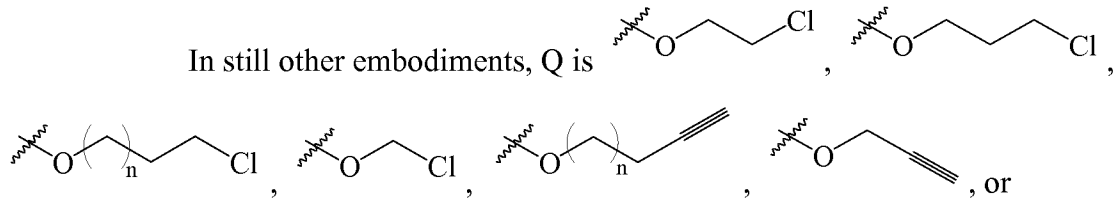


; T is

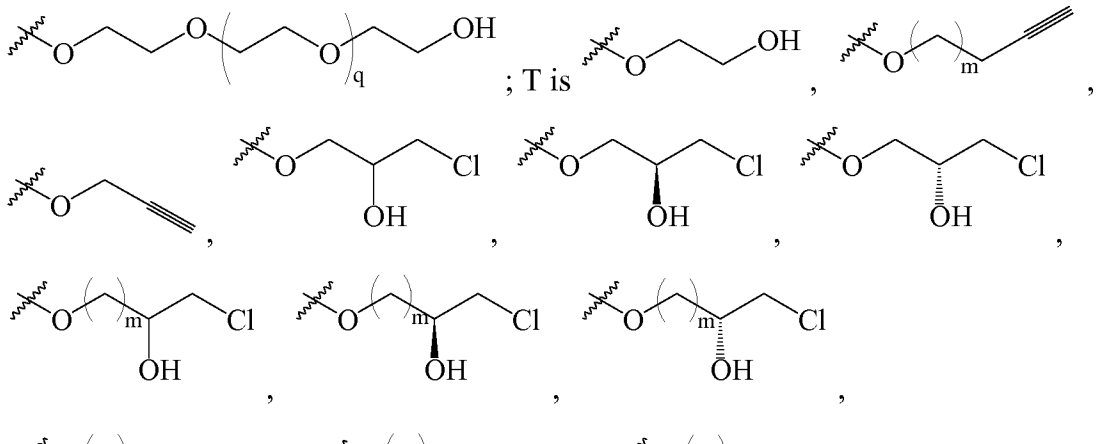


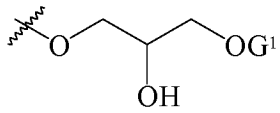
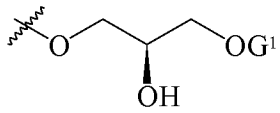
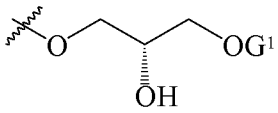
; n is 0, 1, 2, 3, 4, 5, 6, 7 or 8; m is 0, 1, 2, 3, 4, 5, 6, 7 or 8; and each G^1 is independently linear or branched, substituted or unsubstituted, saturated or unsaturated C_1-C_{10} alkyl, wherein the optional substituents are selected from oxo, OJ′″, COOH, OH, F, Cl, Br, I, NH_2, CN, SH, SO_3H, $CONH_2$, OPO_3H_3, and NO_2.

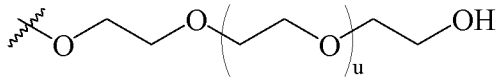
In still other embodiments, Q is

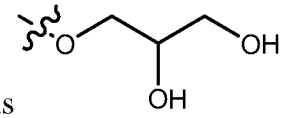


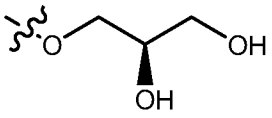
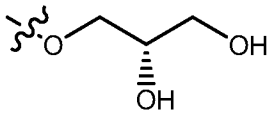
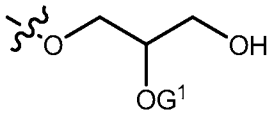
; T is

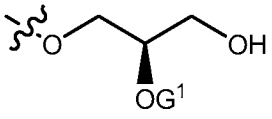
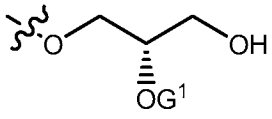
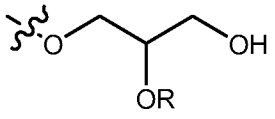


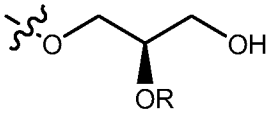
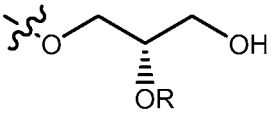
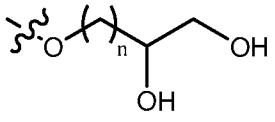



, or

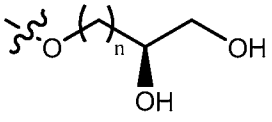
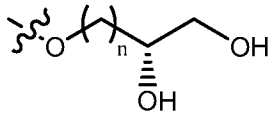
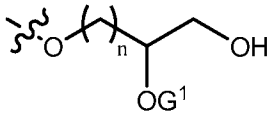

; n is 0, 1, 2, 3, 4, 5, 6, 7 or 8; q is 0, 1, 2, 3, 4, 5, 6 or 7; m is 0, 1, 2, 3, 4, 5, 6, 7 or 8; u is 0, 1, 2, 3, 4, 5, 6 or 7; and each G^1 is independently linear or branched, substituted or unsubstituted, saturated or unsaturated C_1-C_{10} alkyl, wherein the optional substituents are selected from oxo, OJ′″, COOH, OH, F, Cl, Br, I, NH_2, CN, SH, SO_3H, $CONH_2$, OPO_3H_3, and NO_2.

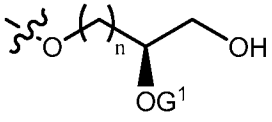
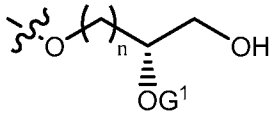
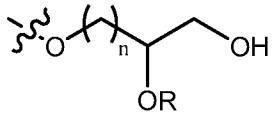
In yet other embodiments, q is  ;

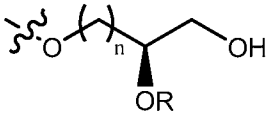
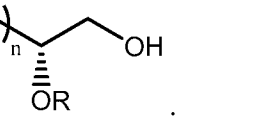
 ;
 ;
 ;

 ;
 ;
 ;

 ;
 ;
 ;

 ;
 ;
 ;

 ;
 ;
 ;

 ;
 ;
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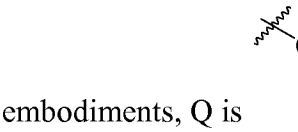
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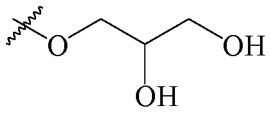
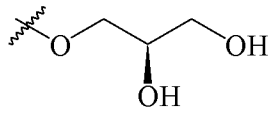
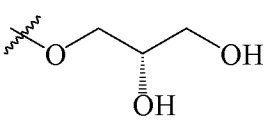
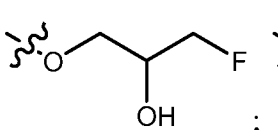
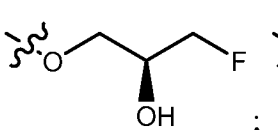
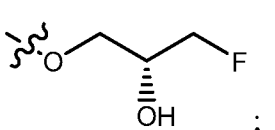
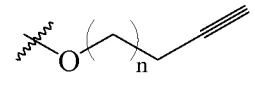
In other embodiments, Q is  ;
 ;

 ;
 ;
 ;
 ;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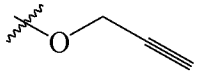
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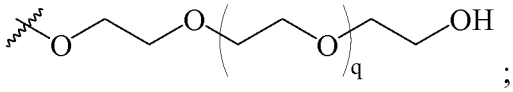
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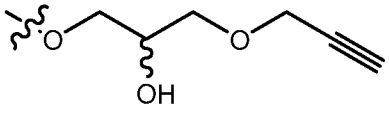
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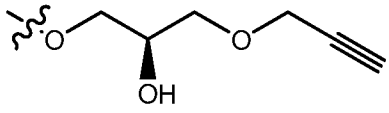
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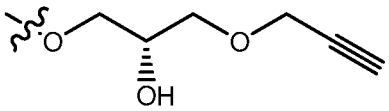
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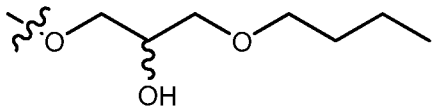
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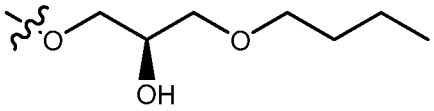
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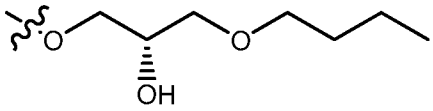
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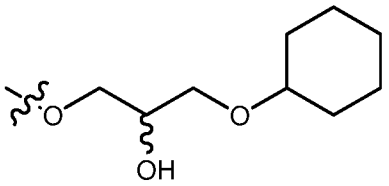
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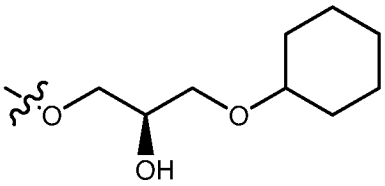
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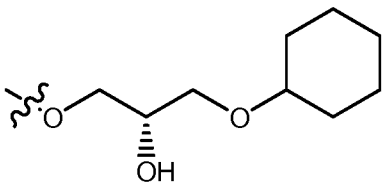
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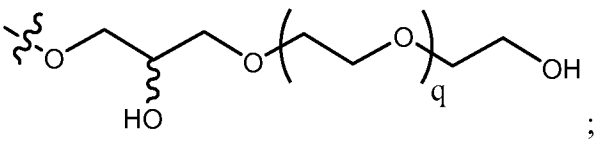
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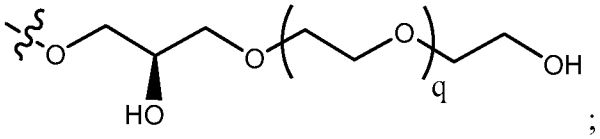
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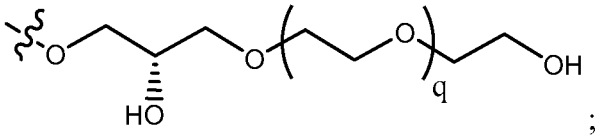
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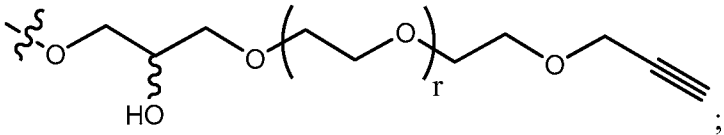
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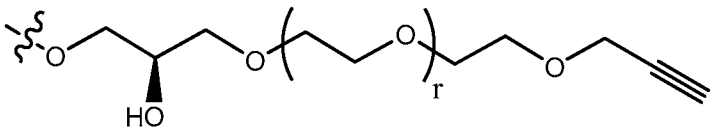
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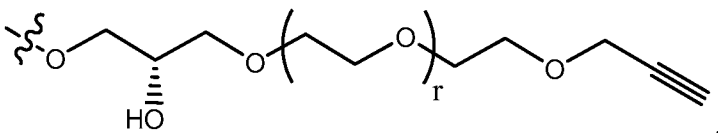
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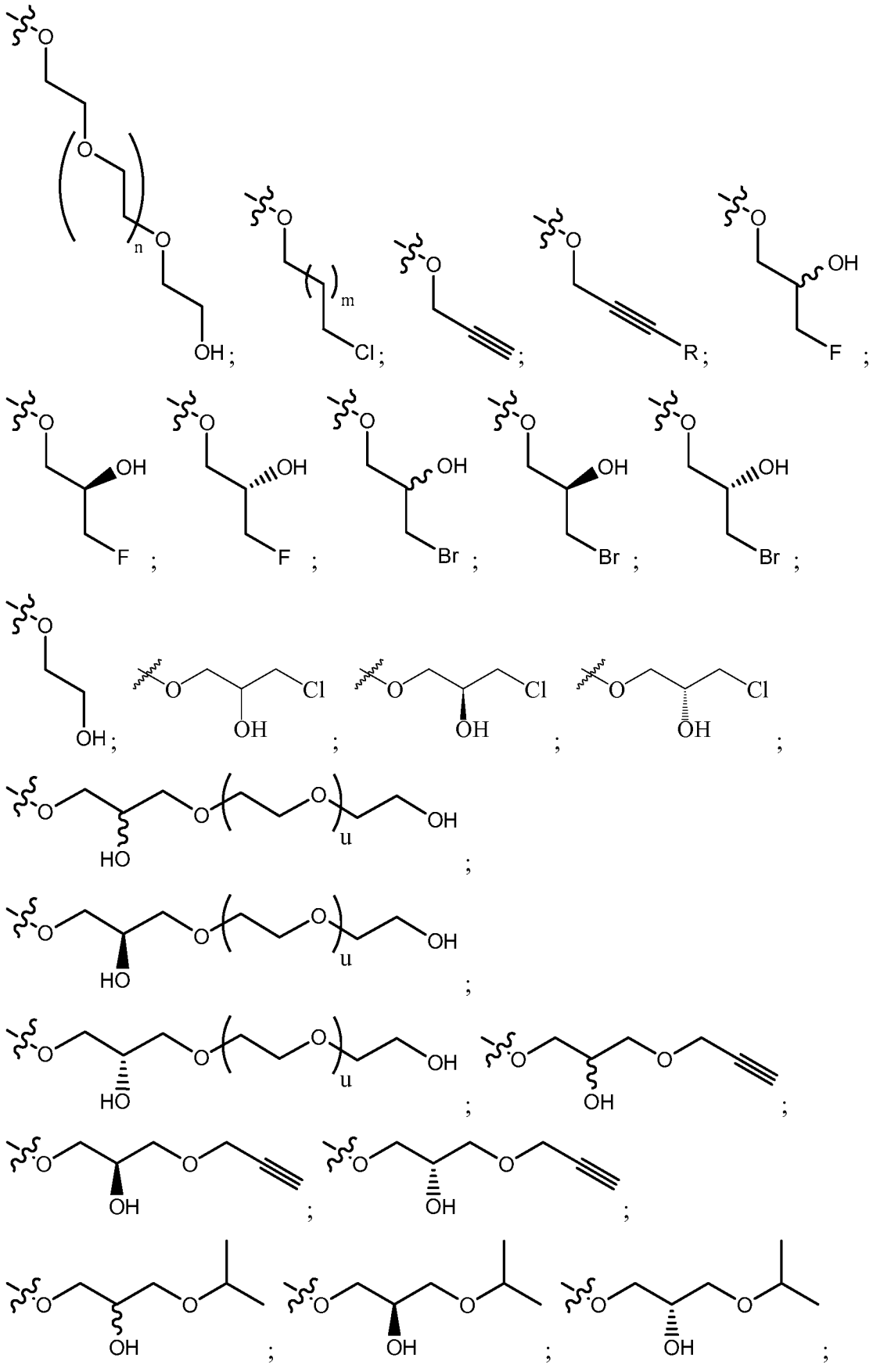

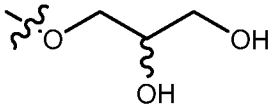
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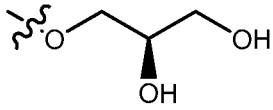
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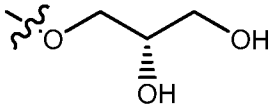
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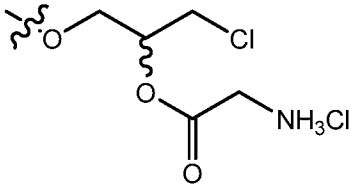
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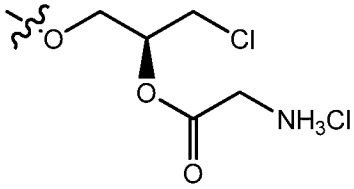
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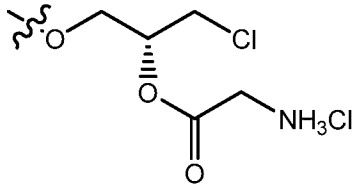
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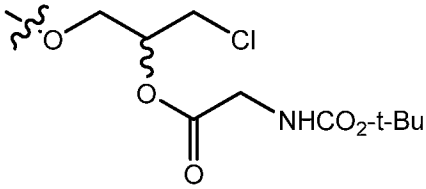
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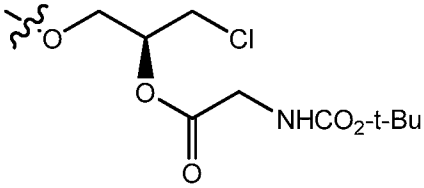
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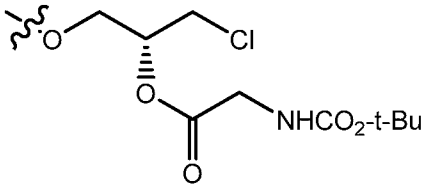
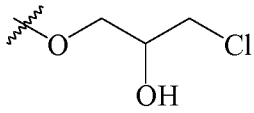

; and n, m and q are each independently 0, 1, 2, 3, 4, 5, 6, 7 or 8.

In still other embodiments, T is 
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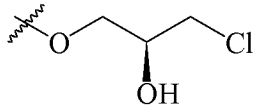
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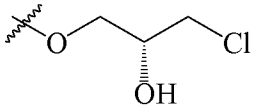
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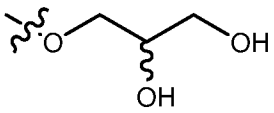
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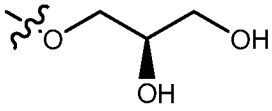
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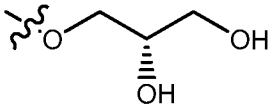
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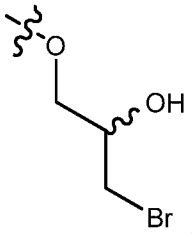
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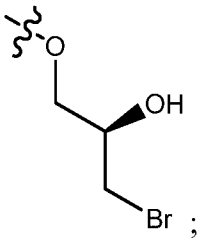
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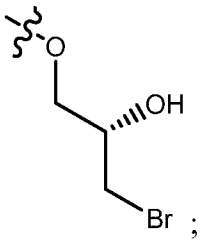
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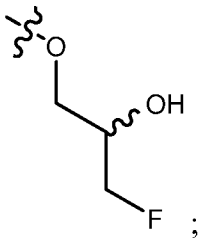
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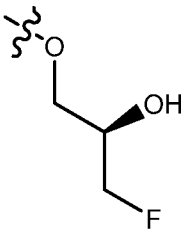
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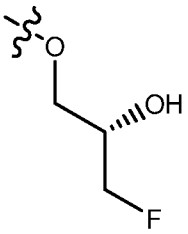
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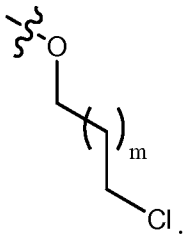
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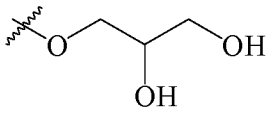
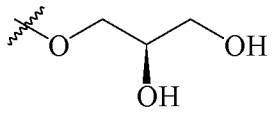
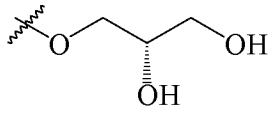
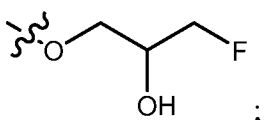
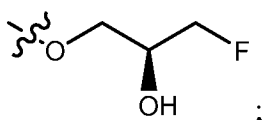
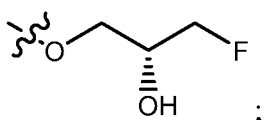
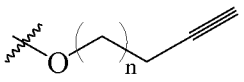
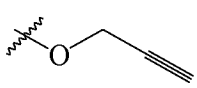
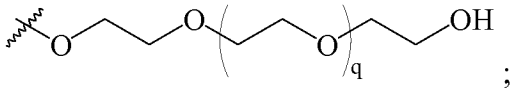
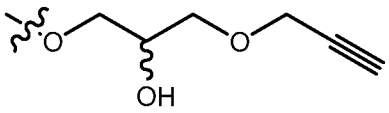
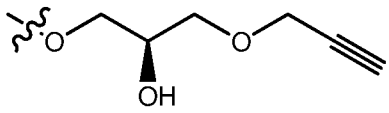
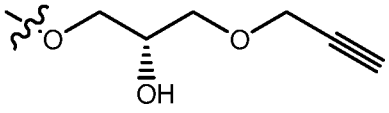
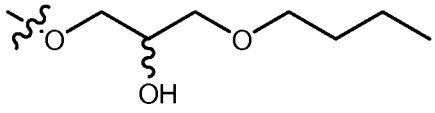
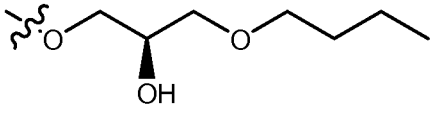
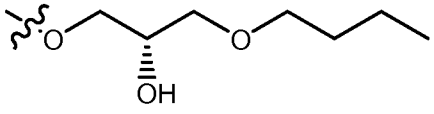
In other examples, Q is  ;  ;

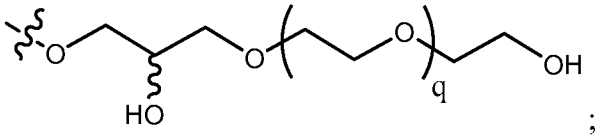
 ;  ;  ;  ;

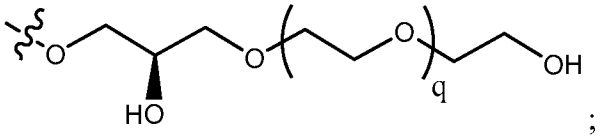
 ,  ;  ;

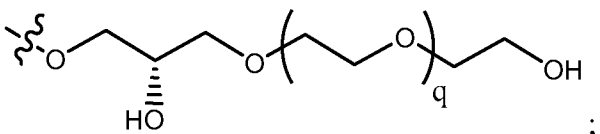
 ;  ;

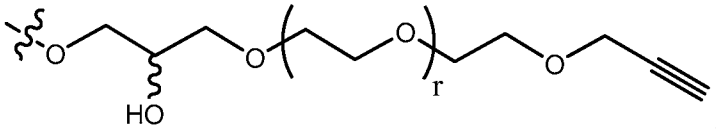
 ;  ;

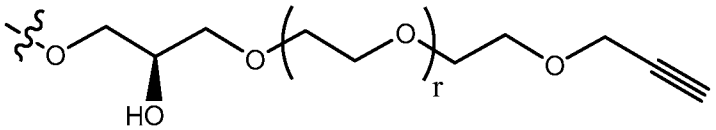
 ;  ;

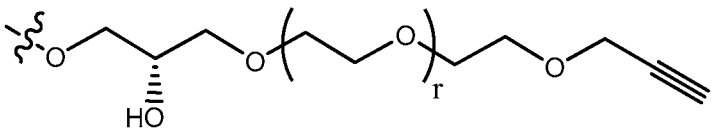
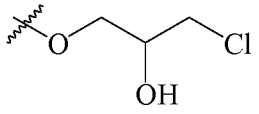
 ;

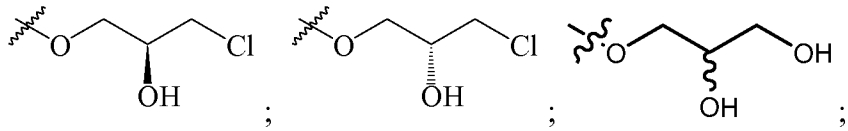
 ;

 ;

 ;

 or

 and T is  ;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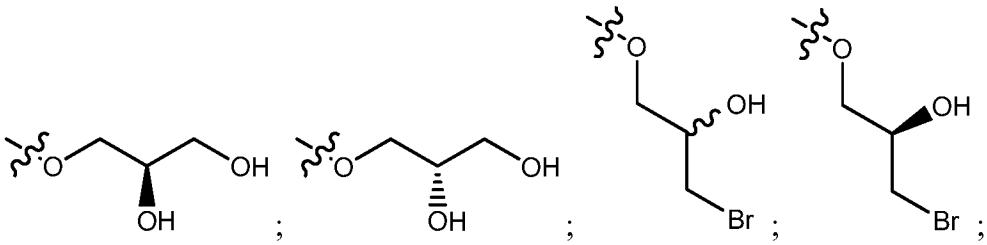
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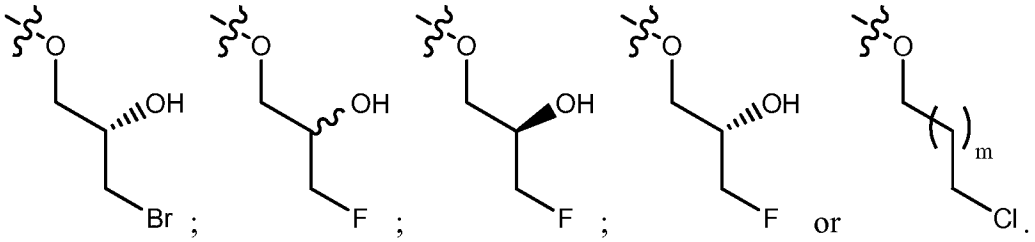
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or

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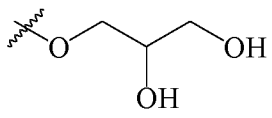
In certain further embodiments, Q is 
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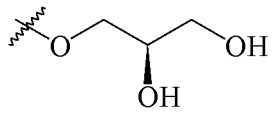
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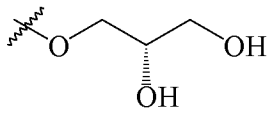
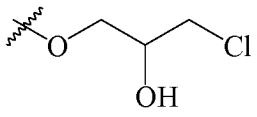

and T is

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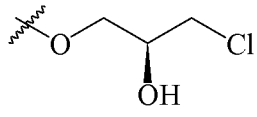
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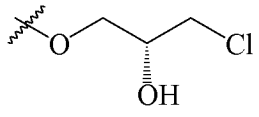
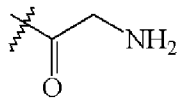

.

In other embodiments, each remaining Z^1, Z^2 and Z^3 is, at each occurrence, independently CCH_3; CH; CF, CCl or CBr. For example in some embodiments, each remaining Z^1, Z^2 and Z^3 is CH.

In some other embodiments, one or more of the OH groups of any one of the foregoing compounds of Formula I is substituted to replace the H with a moiety from TABLE 1. For example in some embodiments, the moiety from TABLE 1 is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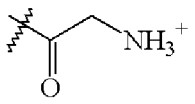
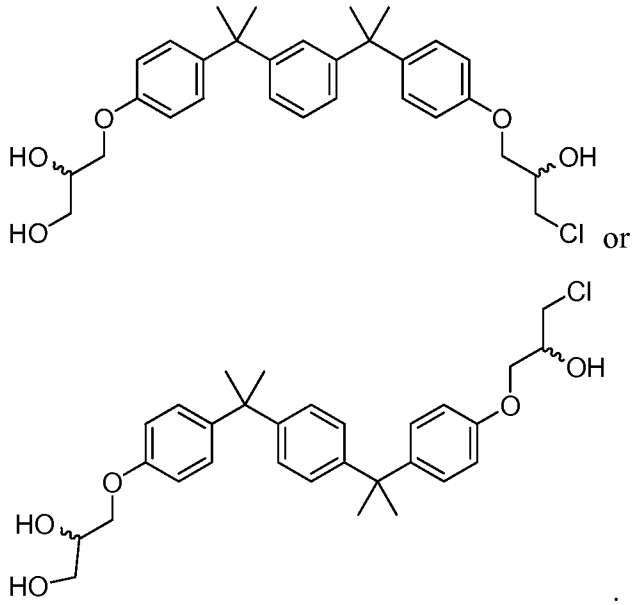
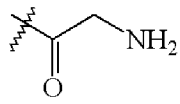
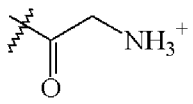

.

In another embodiment, the present disclosure provides a compound having one of the following structures:



. For example, in some other embodiments, one or more of the OH groups of the foregoing compounds is substituted to replace the H with a moiety from TABLE 1. For example in some embodiments, the moiety from TABLE 1 is  or  .

In another embodiment, the present disclosure provides the use of any one of the foregoing compounds for modulating androgen receptor (AR) activity. For example in some embodiments, modulating androgen receptor (AR) activity is in a mammalian cell.

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

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, or pharmaceutically acceptable salt thereof to a subject in need thereof.

In other further embodiments of the foregoing method, modulating androgen receptor (AR) activity is for the treatment of one or more of the following: prostate cancer, breast cancer, ovarian cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, and age-related macular degeneration. For example in some embodiments, the prostate cancer is castration resistant prostate cancer. In other embodiments, the prostate cancer is androgen-dependent prostate cancer, and in other embodiments, the spinal and bulbar muscular atrophy is Kennedy's disease.

In some other embodiments, the present disclosure provides a pharmaceutical composition comprising any one of the foregoing compounds and a pharmaceutically acceptable carrier.

In yet another embodiment, the present disclosure provides a pharmaceutical composition comprising any one of the foregoing compounds, an additional therapeutic agent and a pharmaceutically acceptable carrier. For example, in some embodiments, the additional therapeutic agent is for treating prostate cancer, breast cancer, ovarian cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy or age-related macular degeneration.

In other embodiments, the additional therapeutic agent is MDV3100 , 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.

In another embodiment, the present disclosure provides the use of any one of the foregoing pharmaceutical compositions for modulating androgen receptor (AR) activity. For example in some embodiments, modulating androgen receptor (AR) activity is in a mammalian cell.

In other embodiments, modulating androgen receptor (AR) activity is for treatment of at least one indication selected from the group consisting of: prostate cancer, breast cancer, ovarian cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty,

spinal and bulbar muscular atrophy, and age-related macular degeneration. For example in some embodiments, the indication is prostate cancer. For example, in some embodiments, the prostate cancer is castration resistant prostate cancer, and in other embodiments the prostate cancer is androgen-dependent prostate cancer. In still other embodiments, the spinal and bulbar muscular atrophy is Kennedy's disease.

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

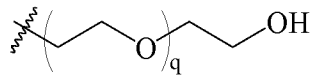
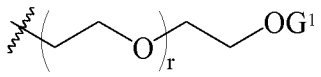
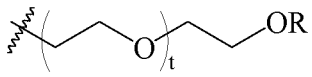
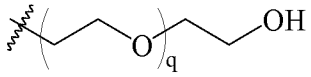
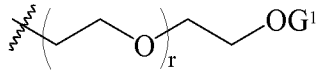
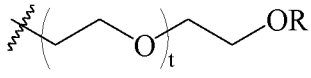
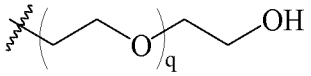
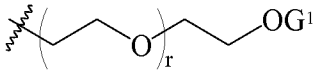
Each J may independently be G^1, O, CH_2, CHG^1, CG^1_2, S, NH, NG^1, SO, SO_2, or NR. Each J may independently be G^1, O, CH_2, CHG^1, CG^1_2, S, NH, or NG^1. Each J may independently be O, S, NH, NG^1, SO, SO_2, or NR. Each J may independently be O, S, SO, or SO_2. Each J may independently be O, NH, NG^1, or NR. Each J may independently be S, NH, NG^1, SO, SO_2, or NR. Each J may independently be S, SO, or SO_2. Each J may independently be NH, NG^1, or NR. Each J may independently be G^1, CH_2, CHG^1, or CG^1_2. Each J may independently be O, CH_2, S, or NH. Each J may independently be O, CH_2, or NH. Each J may independently be O, or CH_2. Each J may independently be G^1, O, CHG^1, or NH. Each J may independently be G^1, O, or CHG^1. Each J may independently be G^1, or O. Each J may independently be O, or S. Each J may independently be G^1. Each J may independently be CH_2. Each J may be CHG^1. Each J may be CG^1_2. Each J may be NR. Each J may be SO_2. Each J may be SO. Each J may be NG^1. Each J may be NH. Each J may be S. Each J may be O.

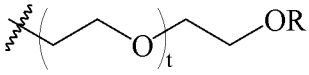
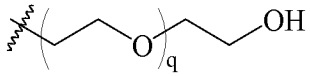
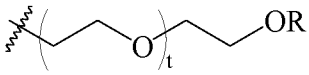
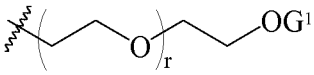
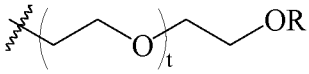
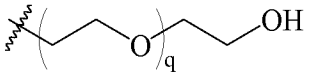
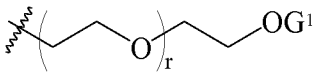
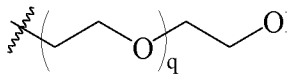
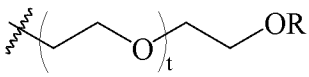
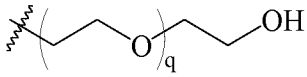
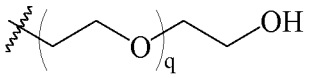
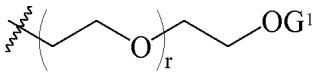
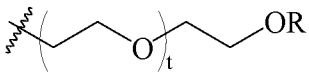
Each M may independently be H, Cl, Br, CH_2OH, CH_2OD, CH_2OG^1, CH_2F, CH_2Cl, $CHCl_2$, CCl_3, CH_2Br, $CHBr_2$, CBr_3, or C≡CH. Each M may

independently be Cl, Br, CH_2OH, CH_2OD, CH_2OG^1, CH_2F, CH_2Cl, $CHCl_2$, CCl_3, CH_2Br, $CHBr_2$, or CBr_3. Each M may independently be Cl, CH_2Cl, $CHCl_2$, or CCl_3. Each M may independently be Br, CH_2Br, $CHBr_2$, or CBr_3. Each M may independently be Cl, or Br. Each M may independently be CH_2Cl, or CH_2Br. Each M may independently be $CHCl_2$, or $CHBr_2$. Each M may independently be CCl_3, or CBr_3. Each M may independently be CH_2Cl, $CHCl_2$, or CCl_3. Each M may independently be CH_2Br, $CHBr_2$, or CBr_3. Each M may independently be Cl, CH_2Cl, or $CHCl_2$. Each M may independently be Br, CH_2Br, or $CHBr_2$. Each M may independently be CH_2Cl, or $CHCl_2$. Each M may independently be CH_2Br, or $CHBr_2$. Each M may independently be Cl, or CCl_3. Each M may independently be Br, or CBr_3. Each M may be H. Each M may be Cl. Each M may be Br. Each M may be $CHCl_2$. Each M may be CCl_3. Each M may be CH_2Br. Each M may be $CHBr_2$. Each M may be CBr_3. Each M may be C≡CH. Each M may be CH_2Cl. Each M may be CH_2F. Each M may be CH_2OH. Each M may be CH_2OD. Each M may be CH_2OG^1.

Each L may independently be H or A-D. Each L may be H. Each L may be A-D.

Each A may independently be O, S, NH, NG1, N+H2, or N+HG1. Each A may independently be O, NH, or N^+H_2. Each A may independently be O, S, NH, or N^+H_2. Each A may independently be O, S, or NH. Each A may independently be O, or NH. Each A may independently be O, or S. Each A may be S. Each A may be NH. Each A may be NG^1. Each A may be N^+H_2. Each A may be N^+HG^1. Each A may be O.

Each D may independently be H, G^1, R,  ,  ,  , or a moiety selected from TABLE 1. Each D may independently be H, G^1, or R. Each D may independently be H, or R. Each D may independently be G^1, or R. Each D may independently be H, or G^1. Each D may independently be  ,  ,  , or a moiety selected from TABLE 1. Each D may independently be  ,  ,

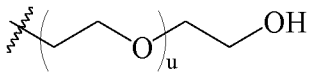
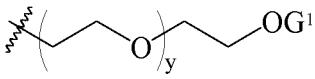
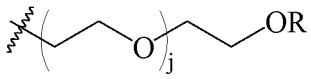
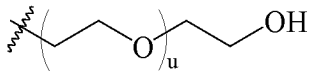
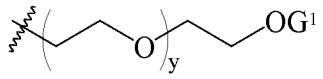
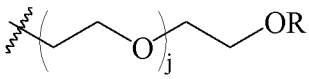
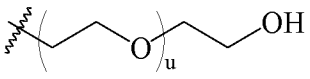
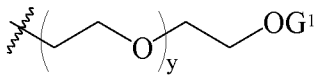
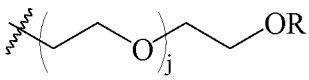
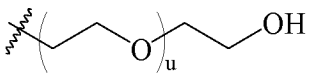
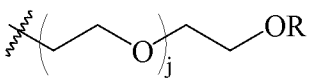
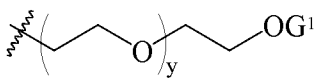
or  . Each D may independently be  , or  . Each D may independently be  , or  . Each D may independently be  , or  . Each D may independently be  ,  , or a moiety selected from TABLE 1. Each D may independently be  , or a moiety selected from TABLE 1. Each D may be H. Each D may be G^1. Each D may be R. Each D may be  . Each D may be  . Each D may be  . Each D may be a moiety selected from TABLE 1.

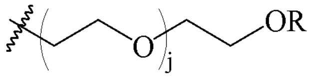
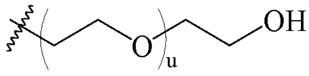
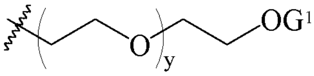
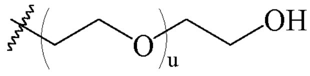
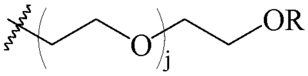
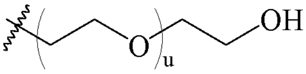
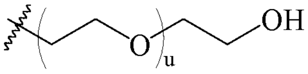
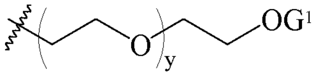
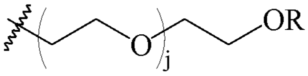
Each J^2 may independently be G^1, O, CH_2, CHG^1, CG^1_2, S, NH, NG^1, SO, SO_2, or NR. Each J^2 may independently be G^1, O, CH_2, CHG^1, CG^1_2, S, NH, or NG^1. Each J^2 may independently be O, S, NH, NG^1, SO, SO_2, or NR. Each J^2 may independently be O, S, SO, or SO_2. Each J^2 may independently be O, NH, NG^1, or NR. Each J^2 may independently be S, NH, NG^1, SO, SO_2, or NR. Each J^2 may independently be S, SO, or SO_2. Each J^2 may independently be NH, NG^1, or NR. Each J^2 may independently be G^1, CH_2, CHG^1, or CG^1_2. Each J^2 may independently be O, CH_2, S, or NH. Each J^2 may independently be O, CH_2, or NH. Each J^2 may independently be O, or CH_2. Each J^2 may independently be G^1, O, CHG^1, or NH. Each J^2 may independently be G^1, O, or CHG^1. Each J^2 may independently be G^1, or O. Each J^2 may independently be O, or S. Each J^2 may independently be G^1. Each J^2 may independently be CH_2. Each J^2 may be CHG^1. Each J^2 may be CG^1_2. Each J^2 may be NR. Each J^2 may be SO_2. Each J^2 may be SO. Each J^2 may be NG^1. Each J^2 may be NH. Each J^2 may be S. Each J^2 may be O.

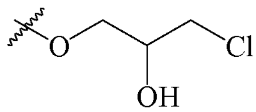
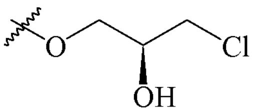
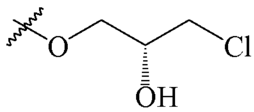
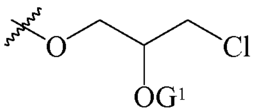
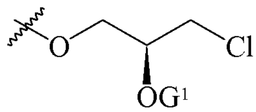
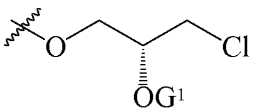
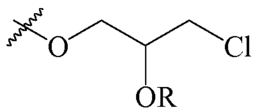
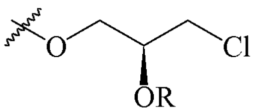
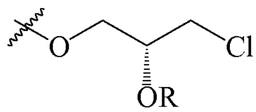
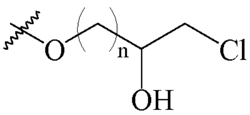
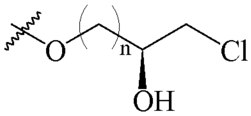
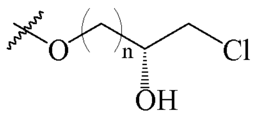
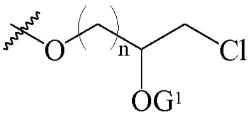
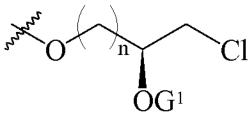
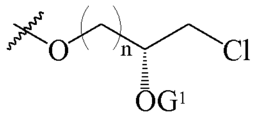
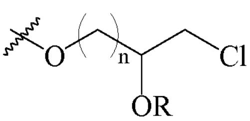
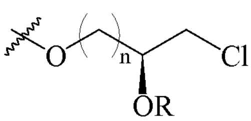
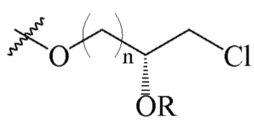
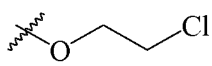
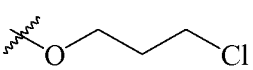
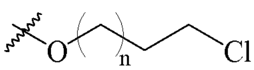
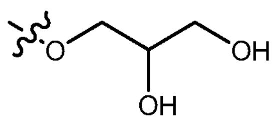
Each M^2 may independently be H, CH_3, Cl, Br, CH_2F, CH_2Cl, $CHCl_2$, CCl_3, CH_2Br, $CHBr_2$, CBr_3, CH_2OH, CH_2OJ'', G^1, CH_2OG^1, CH_2OR, $CH_2OG^1OG^{1\prime}$, $G^1OG^{1\prime}$, $G^1OG^{1\prime}OG^{1\prime\prime}$, CH_2SG^1, CH_2NH_2, CH_2NHG^1, $CH_2NG^1{}_2$, or C≡CH. Each M^2 may independently be H, CH_3, CH_2Cl, CH_2Br, CH_2OJ''', CH_2OG, CH_2OGOG', GOG', $GOG'OG''$, CH_2SG, CH_2NH_2, CH_2NHG, or CH_2NG_2. Each M^2 may independently be H, CH_3, CH_2Cl, CH_2Br, CH_2OJ''', CH_2OG, or CH_2OGOG'. Each M^2 may independently be CH_2Cl, CH_2Br, CH_2OH, CH_2OCH_3, CH_2O(isopropyl), or $CH_2OC_2H_4OC_4H_9$. Each M^2 may independently be H, CH_3, CH_3OCH_3, $CH_3OCH_2CH_3$, CH_2Cl, or CH_2Br. Each M^2 may independently be CH_3, $CH_3OCH_2CH_3$, CH_2Cl, CH_2Br, CH_2OH, CH_2OCH_3, or CH_2O(isopropyl). Each M^2 may independently be CH_3, CH_2Cl, CH_2Br, CH_2OH, $CH_3OCH_2CH_3$, or CH_2OCH_3. Each M^2 may independently be CH_3, CH_2Cl, CH_2Br, CH_2OH, or CH_2OCH_3. Each M^2 may independently be CH_3, CH_2OH, CH_2OCH_3, or $CH_2OCH_2CH_3$. Each M^2 may independently be CH_2Cl, or CH_2Br. Each M^2 may independently be H, Cl, Br, CH_2Cl, $CHCl_2$, CCl_3, CH_2Br, $CHBr_2$, CBr_3, or C≡CH. Each M^2 may independently be Cl, Br, CH_2Cl, $CHCl_2$, CCl_3, CH_2Br, $CHBr_2$, or CBr_3. Each M^2 may independently be Cl, CH_2Cl, $CHCl_2$, or CCl_3. Each M^2 may independently be Br, CH_2Br, $CHBr_2$, or CBr_3. Each M^2 may independently be Cl, or Br. Each M^2 may independently be CH_2Cl, or CH_2Br. Each M^2 may independently be $CHCl_2$, or $CHBr_2$. Each M^2 may independently be CCl_3, or CBr_3. Each M^2 may independently be CH_2Cl, $CHCl_2$, or CCl_3. Each M^2 may independently be CH_2Br, $CHBr_2$, or CBr_3. Each M^2 may independently be Cl, CH_2Cl, or $CHCl_2$. Each M^2 may independently be Br, CH_2Br, or $CHBr_2$. Each M^2 may independently be CH_2Cl, or $CHCl_2$. Each M^2 may independently be CH_2Br, or $CHBr_2$. Each M^2 may independently be Cl, or CCl_3. Each M^2 may independently be Br, or CBr_3. Each M^2 may be H. Each M^2 may be CH_3. Each M^2 may be Cl. Each M^2 may be Br. Each M^2 may be CH_2Cl. Each M^2 may be $CHCl_2$. Each M^2 may be CCl_3. Each M^2 may be CH_2Br. Each M^2 may be $CHBr_2$. Each M^2 may be CBr_3. Each M^2 may be CH_2OH. Each M^2 may be CH_2OJ''. Each M^2 may be G^1. Each M^2 may be CH_2OG^1. Each M^2 may be CH_2OR. Each M^2 may be $CH_2OG^1OG^{1\prime}$. Each M^2 may be $G^1OG^{1\prime}$. Each M^2 may be $G^1OG^{1\prime}OG^{1\prime\prime}$. Each M^2 may be CH_2SG^1. Each M^2 may be CH_2NH_2. Each M^2 may be CH_2NHG^1. Each M^2 may be $CH_2NG^1{}_2$. Each M^2 may be C≡CH. Each M^2 may be CH_2F.

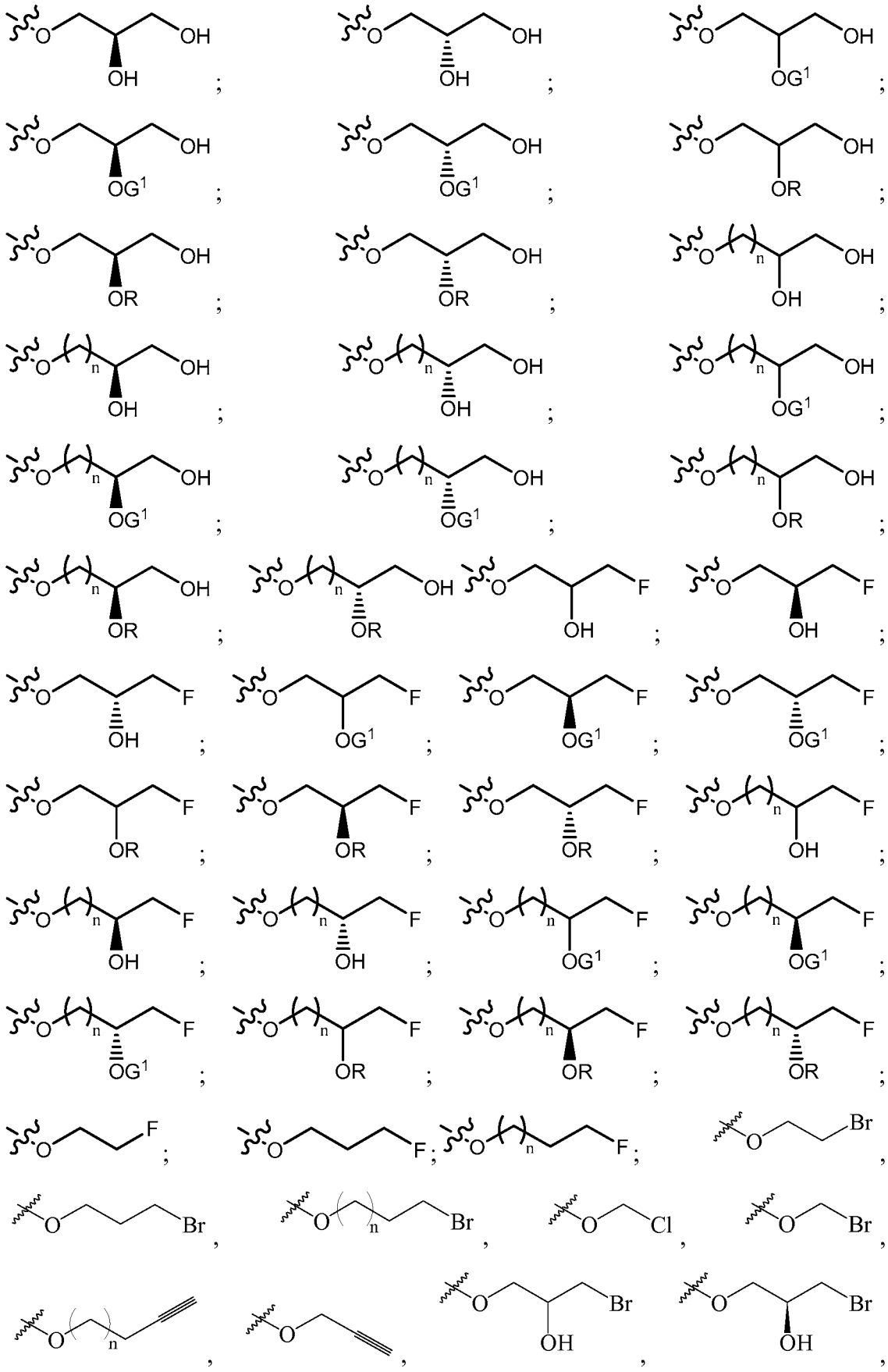
Each L^2 may independently be H or A^2-D^2. Each L^2 may be H. Each L^2 may be A^2-D^2.

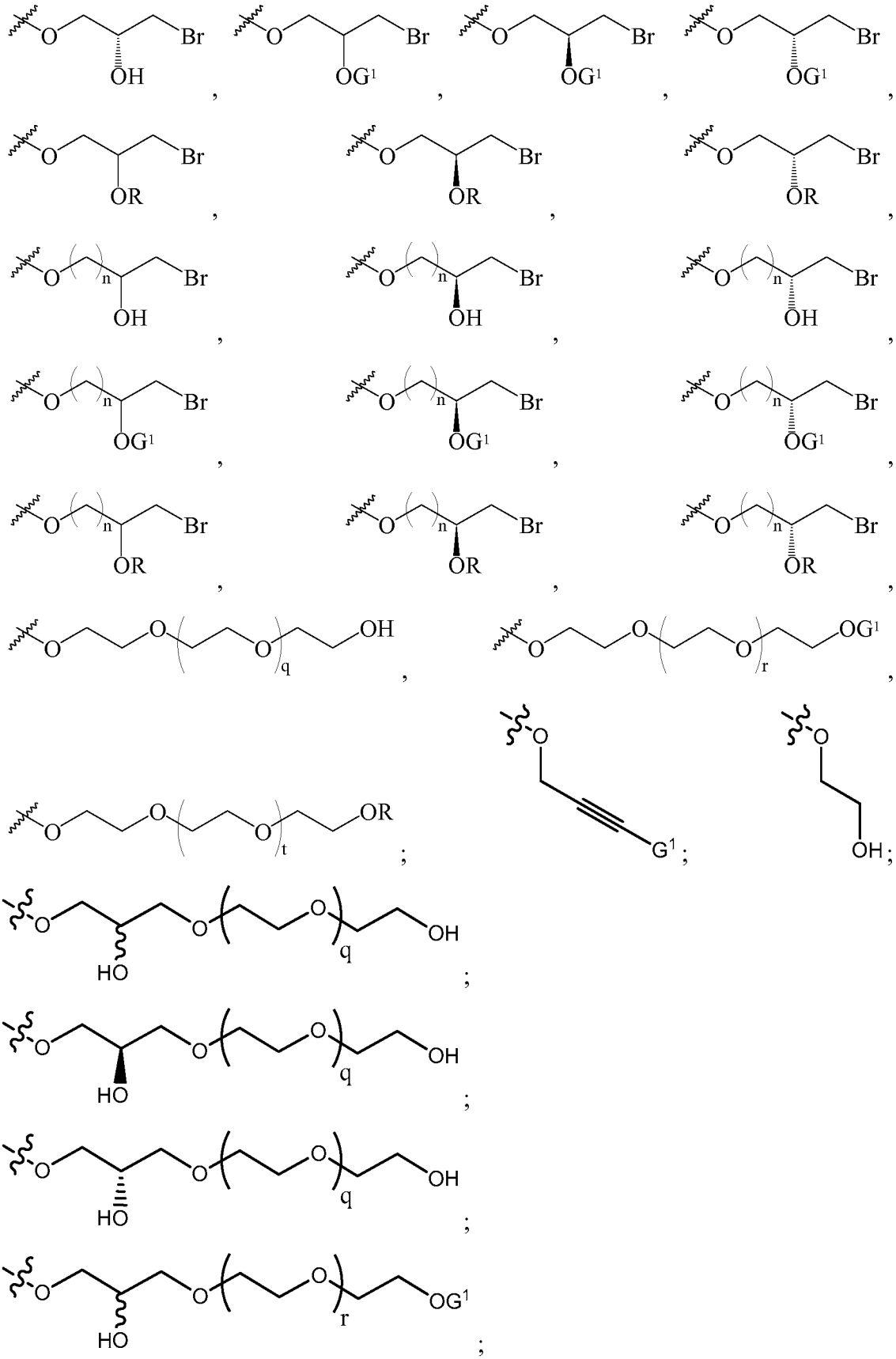
Each A^2 may independently be O, S, SO, SO_2, NH, NG^1, N^+H_2, or N^+HG^1. Each A^2 may independently be O, S, SO, or SO_2. Each A^2 may independently be O, NH, NG^1, N^+H_2, or N^+HG^1. Each A^2 may independently be S, SO, SO_2, NH, NG^1, N^+H_2, or N^+HG^1. Each A^2 may independently be O, S, SO, SO_2, NH, or N^+H_2. Each A^2 may independently be S, SO, or SO_2. Each A^2 may independently be NH, NG^1, N^+H_2, or N^+HG^1. Each A^2 may independently be NH, or N^+H_2. Each A^2 may independently be O, S, NH, NG^1, N^+H_2, or N^+HG^1. Each A^2 may independently be O, NH, or N^+H_2. Each A^2 may independently be O, S, NH, or N^+H_2. Each A^2 may independently be O, S, or NH. Each A^2 may independently be O, or NH. Each A^2 may independently be O, or S. Each A^2 may be S. Each A^2 may be SO. Each A^2 may be SO_2. Each A^2 may be NH. Each A^2 may be NG^1. Each A^2 may be N^+H_2. Each A^2 may be N^+HG^1. Each A^2 may be O.

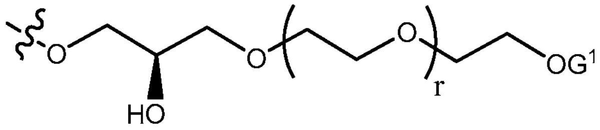
Each D^2 may independently be H, G^1, R,  ,  ,  , or a moiety selected from TABLE 1. Each D^2 may independently be H, G^1, or R. Each D^2 may independently be H, or R. Each D^2 may independently be G^1, or R. Each D^2 may independently be H, or G^1. Each D^2 may independently be  ,  ,  , or a moiety selected from TABLE 1. Each D^2 may independently be  ,  , or  . Each D^2 may independently be  , or  . Each D^2 may independently be  ,

or  . Each D^2 may independently be  , or  . Each D^2 may independently be  ,  , or a moiety selected from TABLE 1. Each D^2 may independently be  , or a moiety selected from TABLE 1. Each D^2 may be H. Each D^2 may be G^1. Each D^2 may be R. Each D^2 may be  . Each D^2 may be  . Each D^2 may be  . Each D^2 may be a moiety selected from TABLE 1.

Each Q may independently be  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ;



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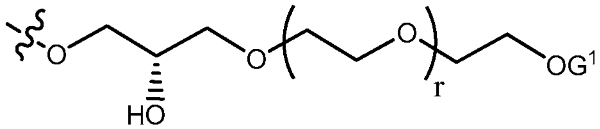
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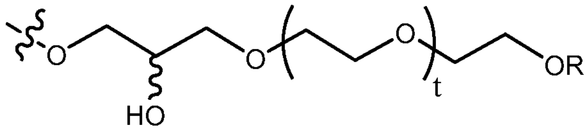
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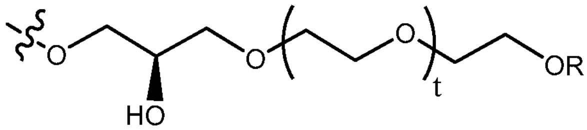
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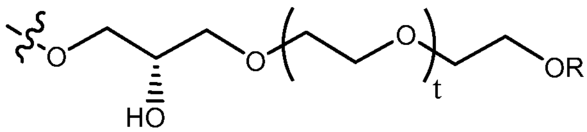
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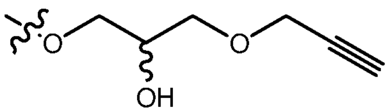
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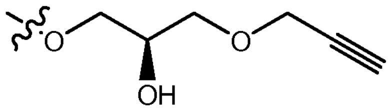
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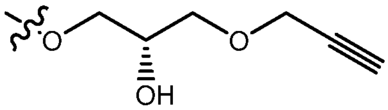
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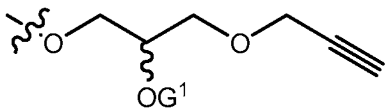
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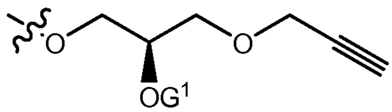
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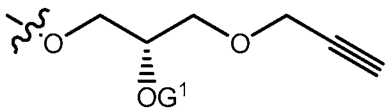
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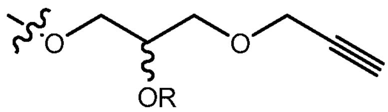
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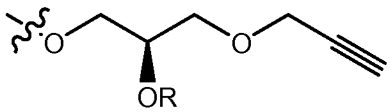
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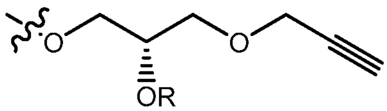
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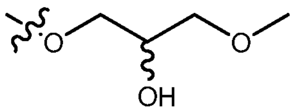
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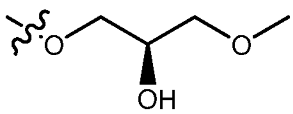
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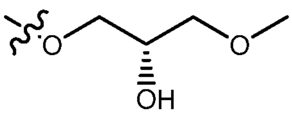
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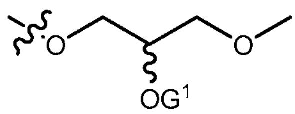
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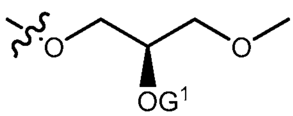
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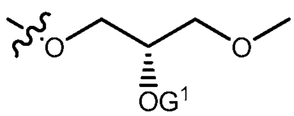
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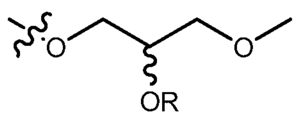
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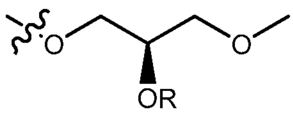
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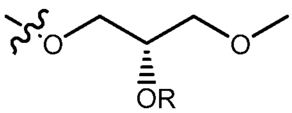
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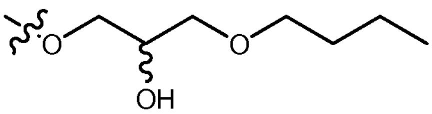
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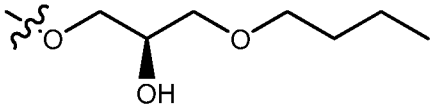
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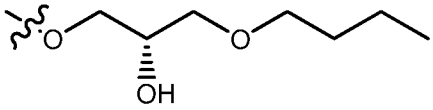
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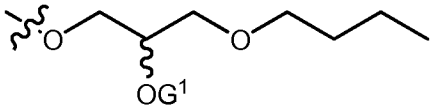
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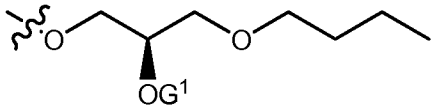
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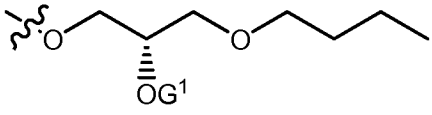
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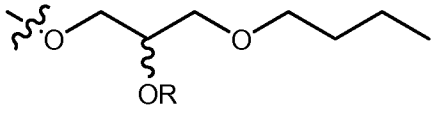
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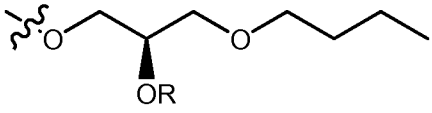
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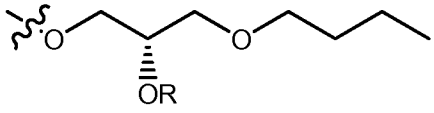
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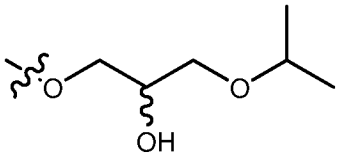
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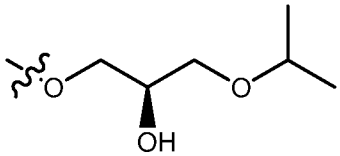
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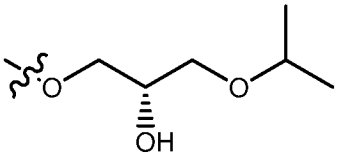
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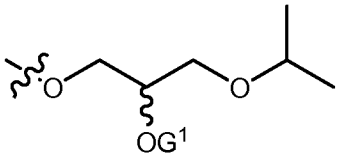
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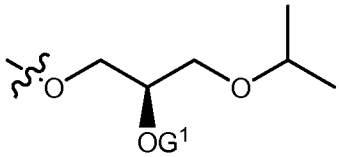
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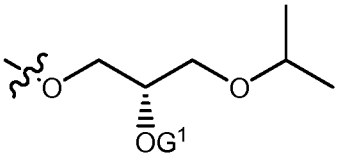
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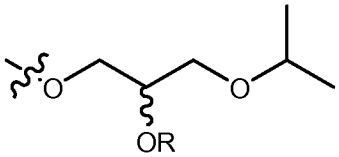
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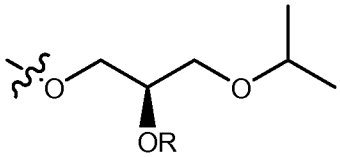
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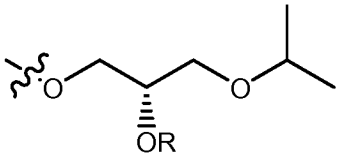
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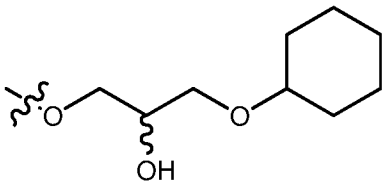
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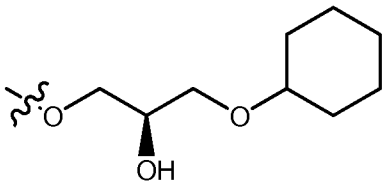
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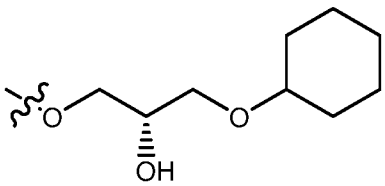
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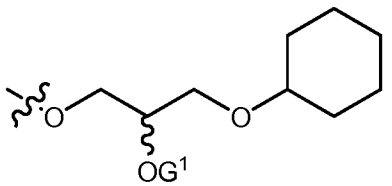
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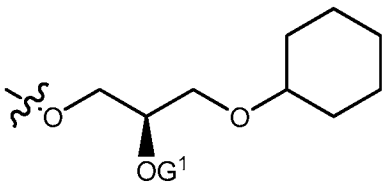

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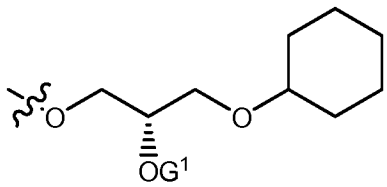

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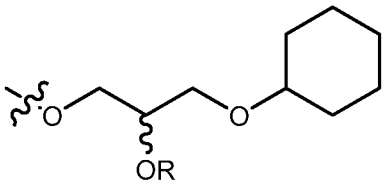

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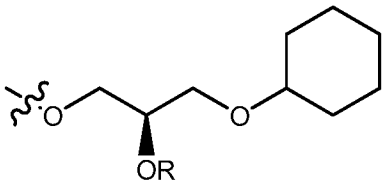

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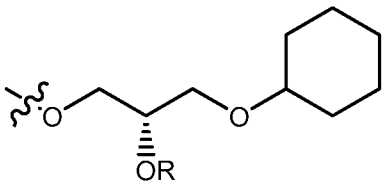

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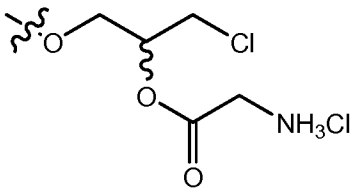

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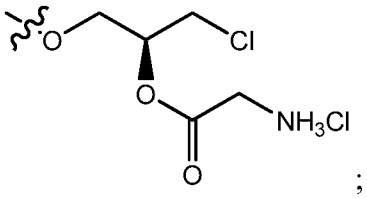

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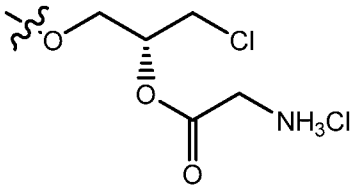

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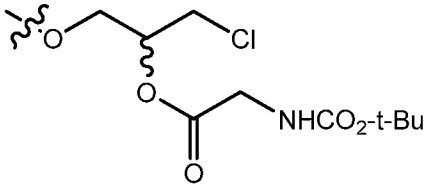

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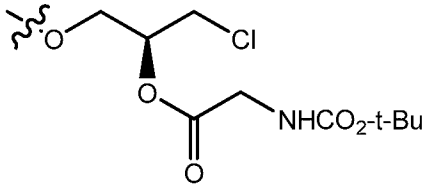

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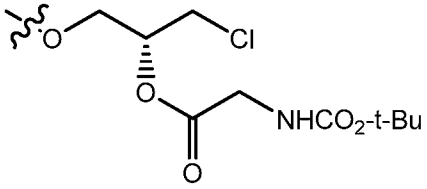

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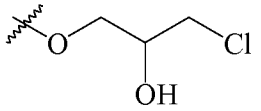
Each Q may independently be 

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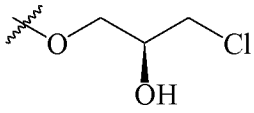

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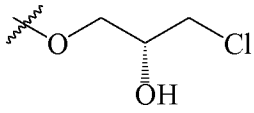

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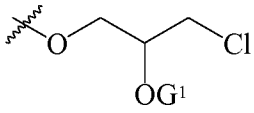

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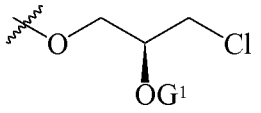

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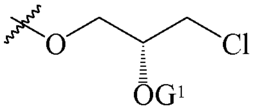
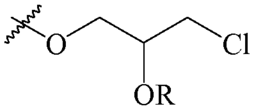
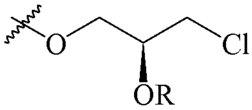
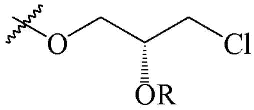
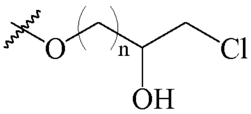
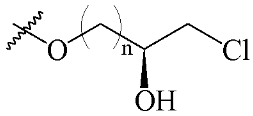
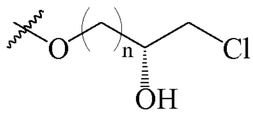
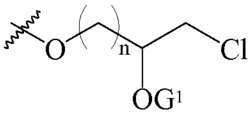
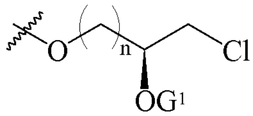
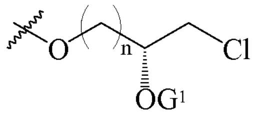
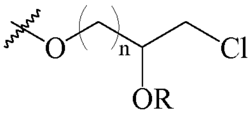
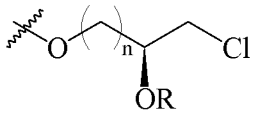
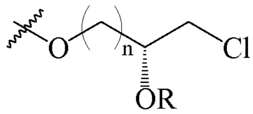
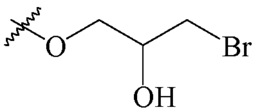
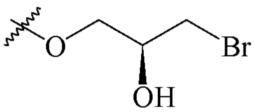
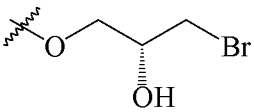
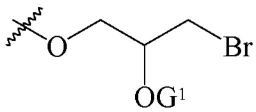
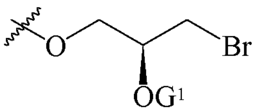
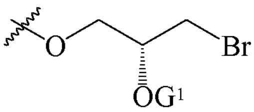
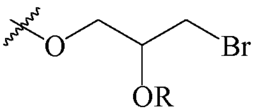
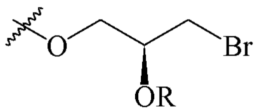
 ,  ,  ,  ,

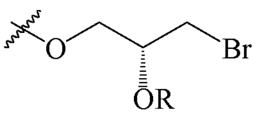
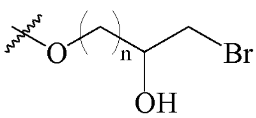
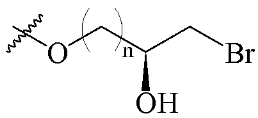
 ,  ,  ,

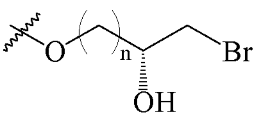
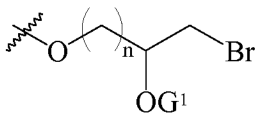
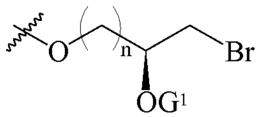
 ,  ,  ,

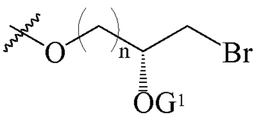
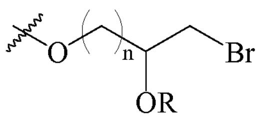
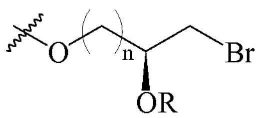
 ,  ,  ,

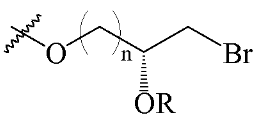
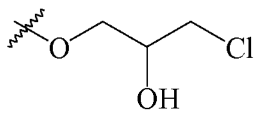
 ,  ,  ,  ,

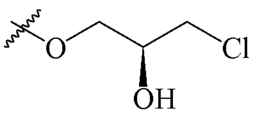
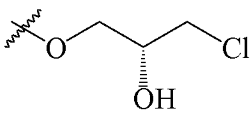
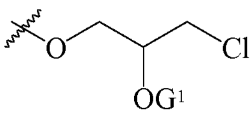
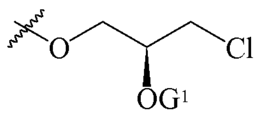
 ,  ,  ,  ,

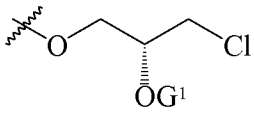
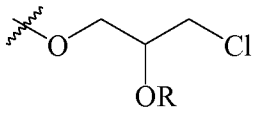
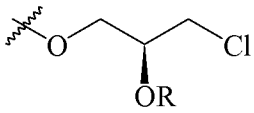
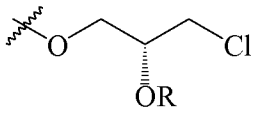
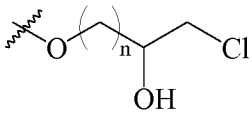
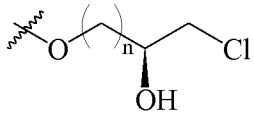
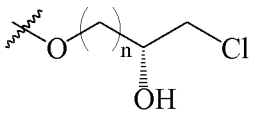
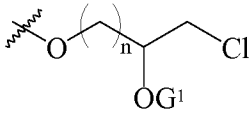
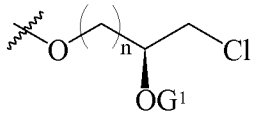
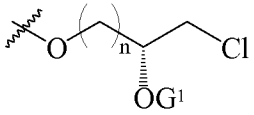
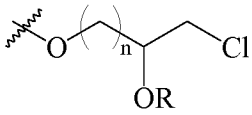
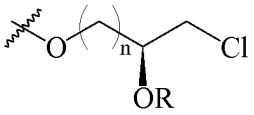
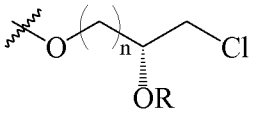
 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

or  . Each Q may independently be  ,

 ,  ,  ,  ,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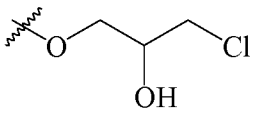
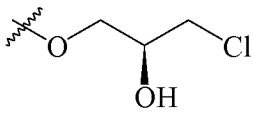
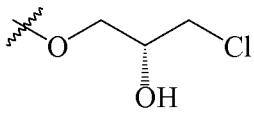
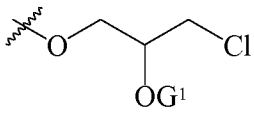
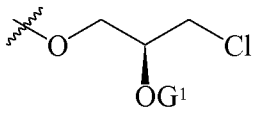
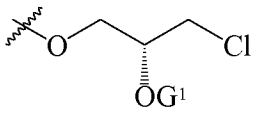
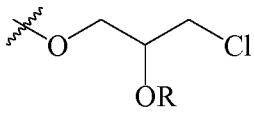
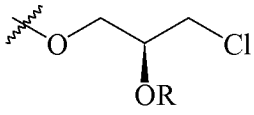
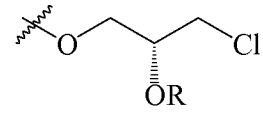
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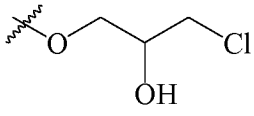
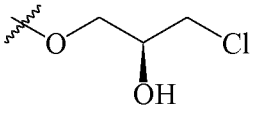
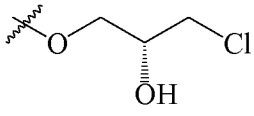
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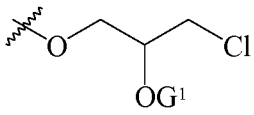
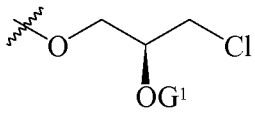
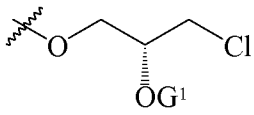
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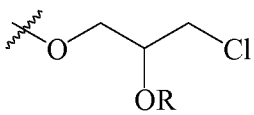
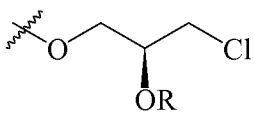
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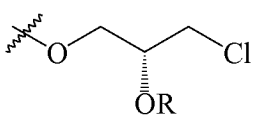
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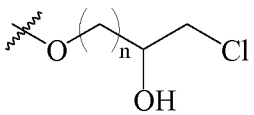
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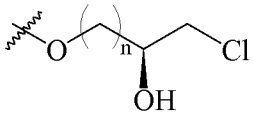
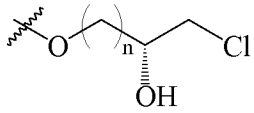
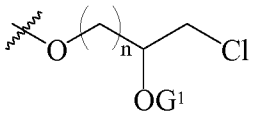
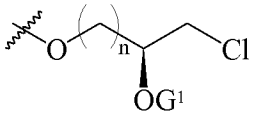
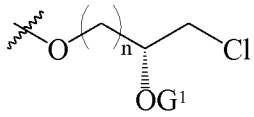
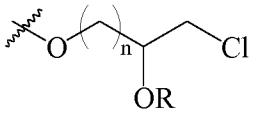
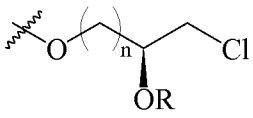
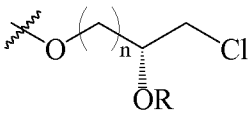

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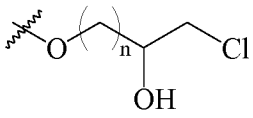
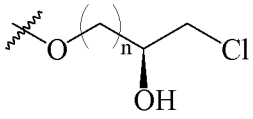
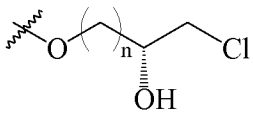

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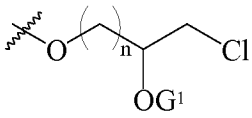
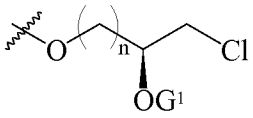
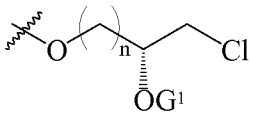

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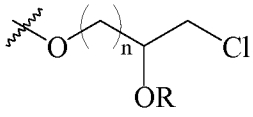
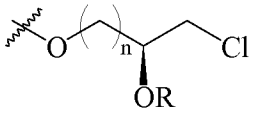

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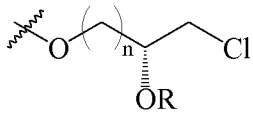
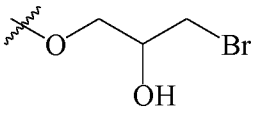

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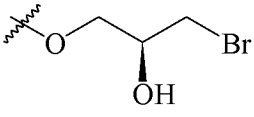
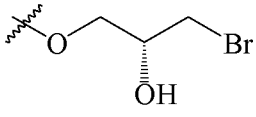
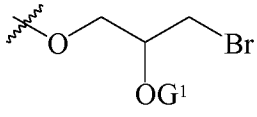
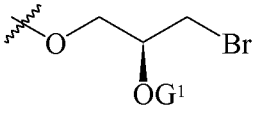
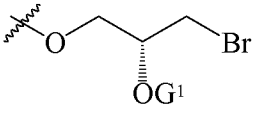
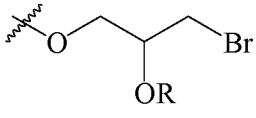
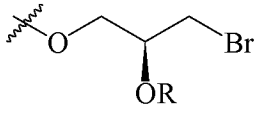
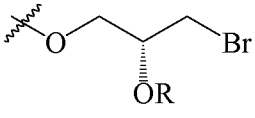
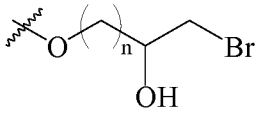
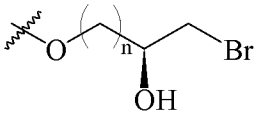
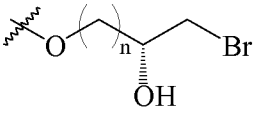
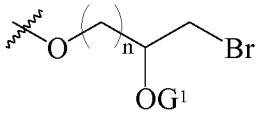
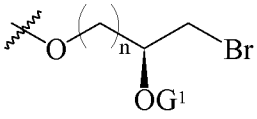
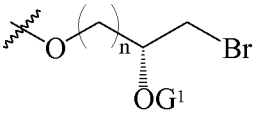

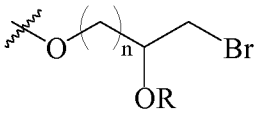
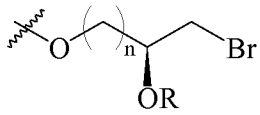
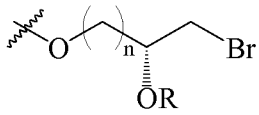
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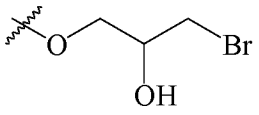
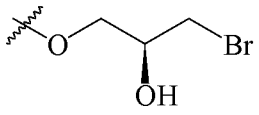
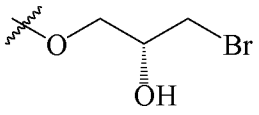
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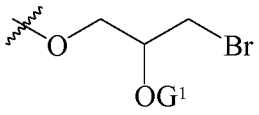
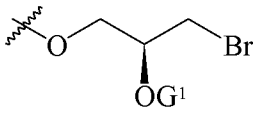
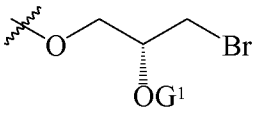
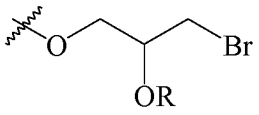
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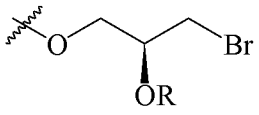
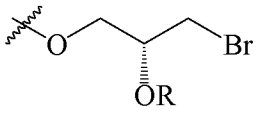
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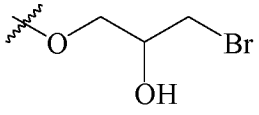
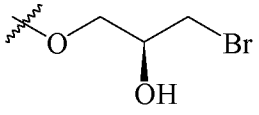
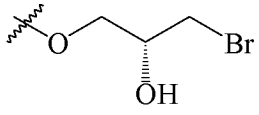
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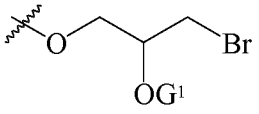
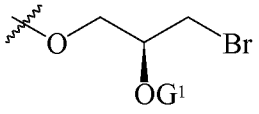
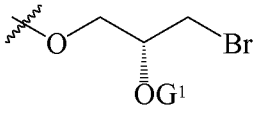
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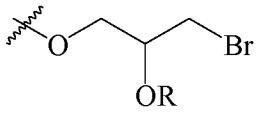
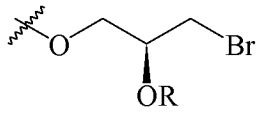
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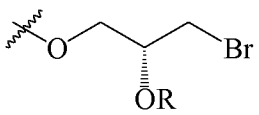
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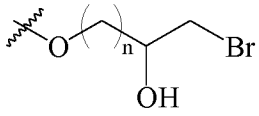
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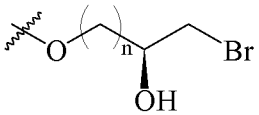
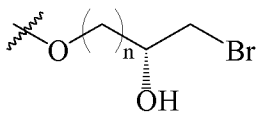
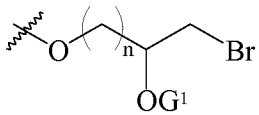
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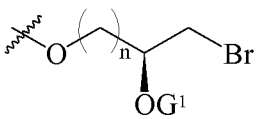
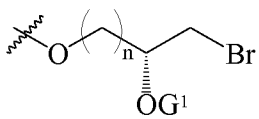
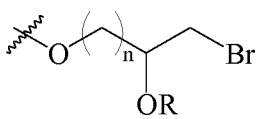
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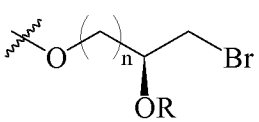
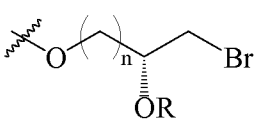
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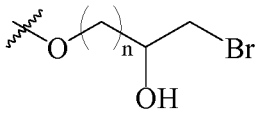
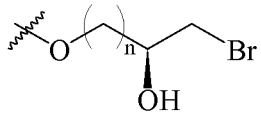
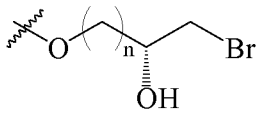
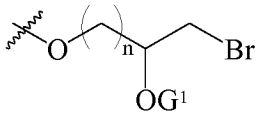
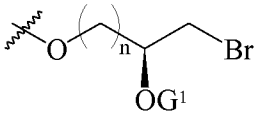
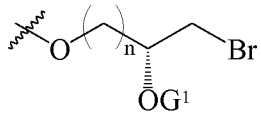
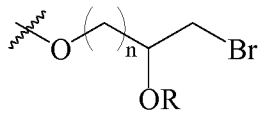
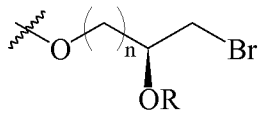
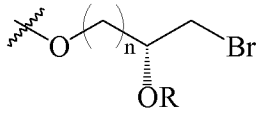
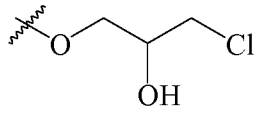
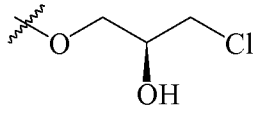
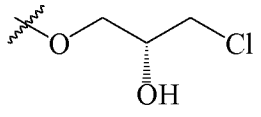
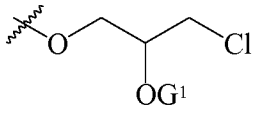
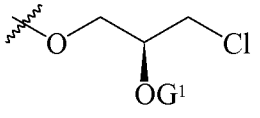
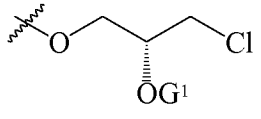
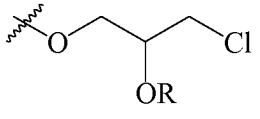
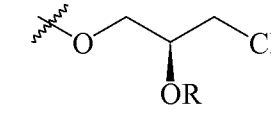
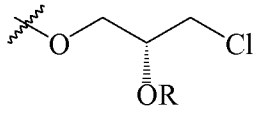
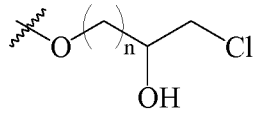
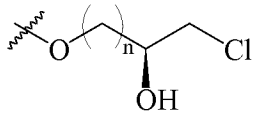
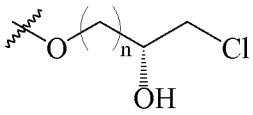
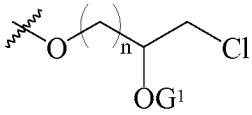
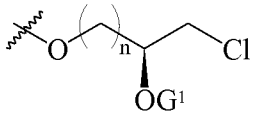
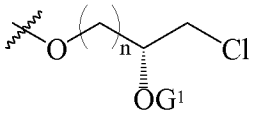
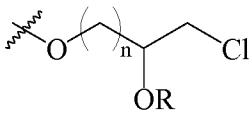
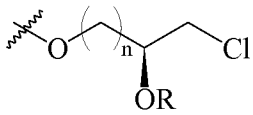
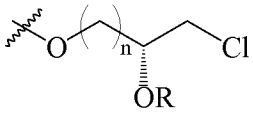
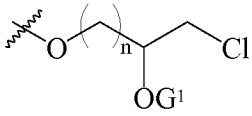
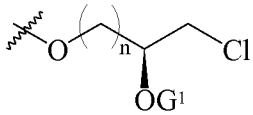
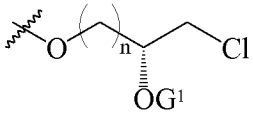
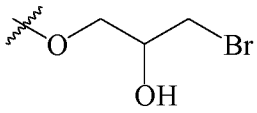
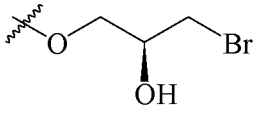
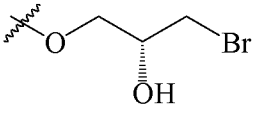
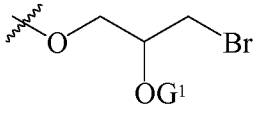
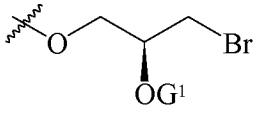
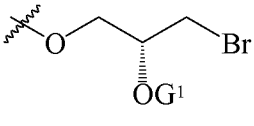
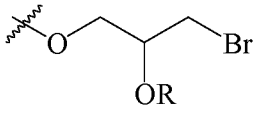
be  ,  , or  . Each Q may independently be  ,  , or  . Each Q may independently be  ,  , or  . Each Q may independently be  . Each Q may independently be  . Each Q may independently be  . Each Q may independently be  . Each Q may independently be  . Each Q may independently be . Each Q may independently be  . Each Q may independently be  . Each Q may independently be  . Each Q may independently be  . Each Q may independently be  . Each Q may independently be  . Each Q may independently be . Each Q may independently be . Each Q may independently be  . Each Q may independently be


. Each Q may independently be 
. Each Q may independently be 
. Each Q may independently be 
. Each Q may independently be 
. Each Q may independently be 
. Each Q may independently be 
. Each Q may independently be 
. Each Q may independently be 
. Each Q may independently be 
. Each Q may independently be 
. Each Q may independently be 
. Each Q may independently be 
. Each Q may independently be 
. Each Q may independently be 
. Each Q may independently be 
. Each Q may independently be 
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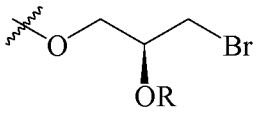
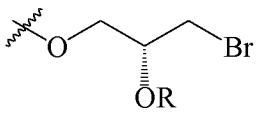
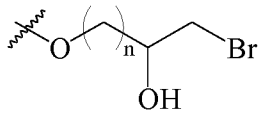
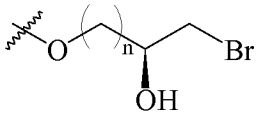
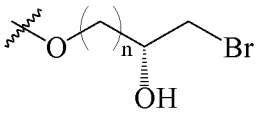
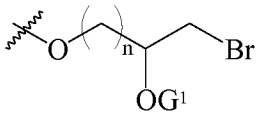
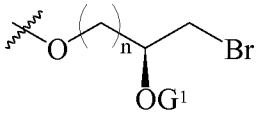
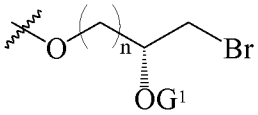
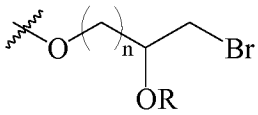
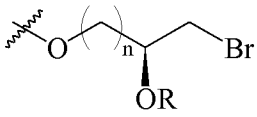
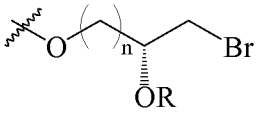
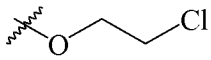
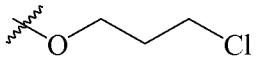
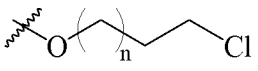
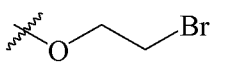
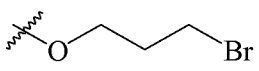
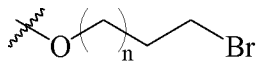
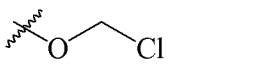
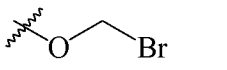
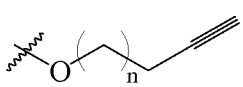
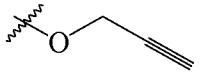
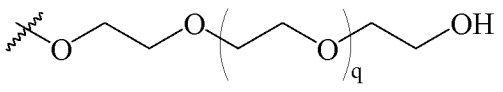
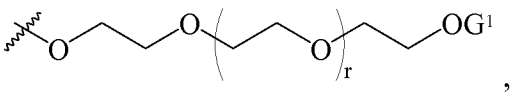
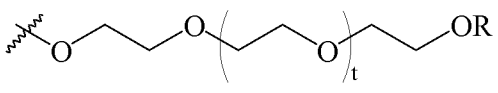
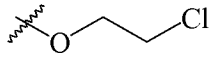
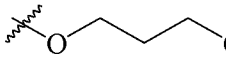
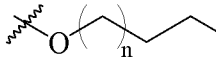
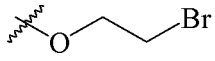
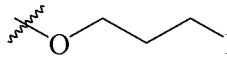
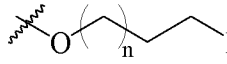
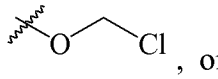
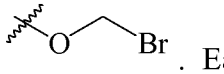
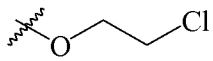
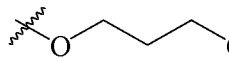
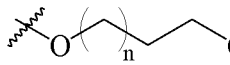
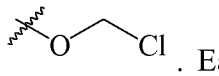
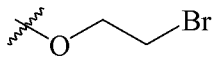
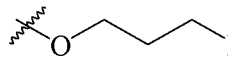
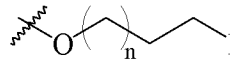
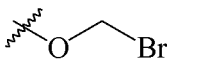
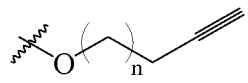
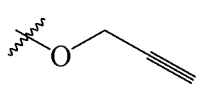
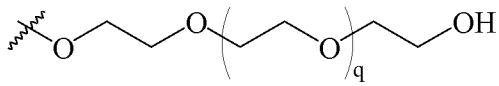
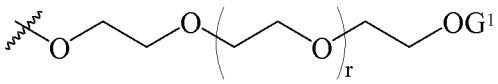
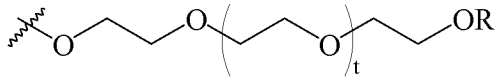
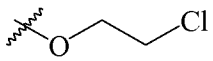
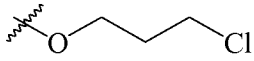
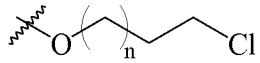
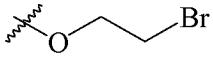
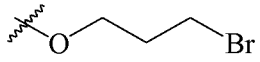
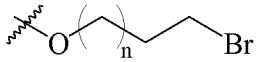
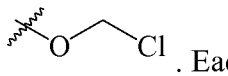
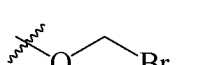
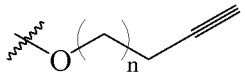
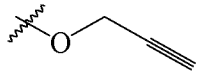
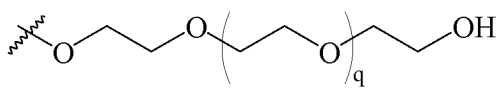
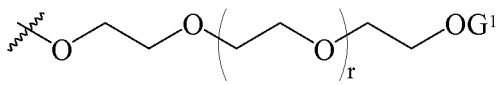
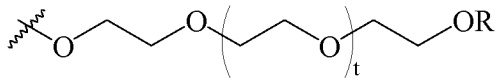
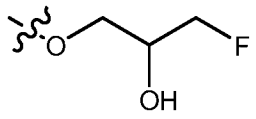
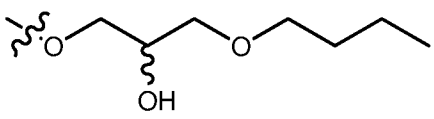
independently be  . Each Q may independently be  . Each Q may independently be  . Each Q may independently be  . Each Q may independently be  . Each Q may independently be  . Each Q may independently be  . Each Q may independently be  . Each Q may independently be  . Each Q may independently be  . Each Q may independently be  .

Each Q may independently be  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  . Each Q may independently be

 ,  ,  ,  ,  ,  ,  or  . Each Q may independently be  ,  ,  , or  . Each Q may independently be  ,  ,  , or  . Each Q may independently be  , or  . Each Q may independently be  ,  , or  . Each Q may be  . Each Q may be  . Each Q may independently be  . Each Q may be  . Each Q may be  . Each Q may independently be  . Each Q may be  . Each Q may be  . Each Q may independently be  . Each Q may be  . Each Q may independently be  . Each Q may independently be  . Each Q may independently be  . Each Q may independently be


. Each Q may independently be 
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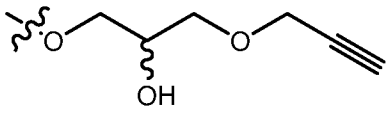
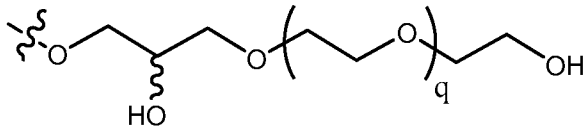
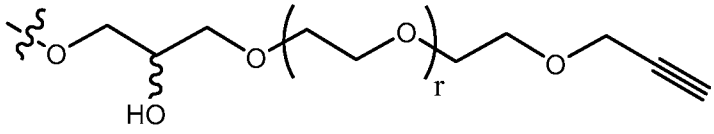
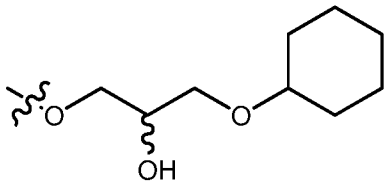
Each Q may independently be 
. Each Q may independently be 
. Each Q may independently be 
. Each Q may independently be 
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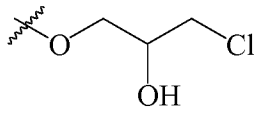
Each T may independently be 
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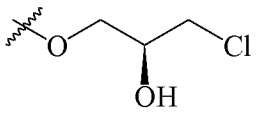
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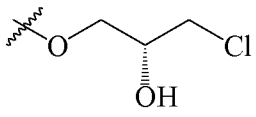
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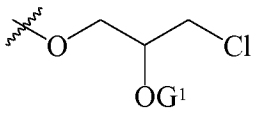
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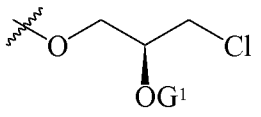
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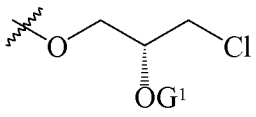
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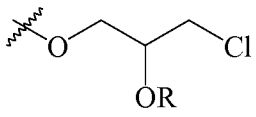
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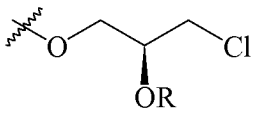
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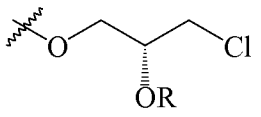
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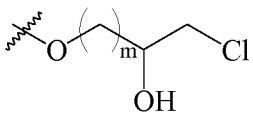
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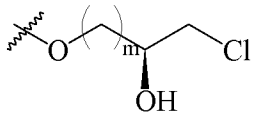
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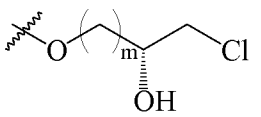
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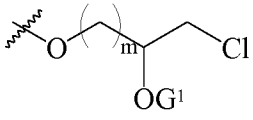
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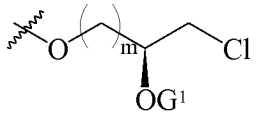
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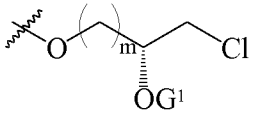
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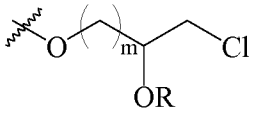
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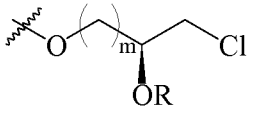
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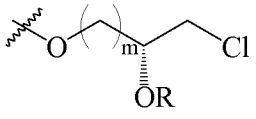
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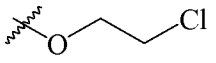
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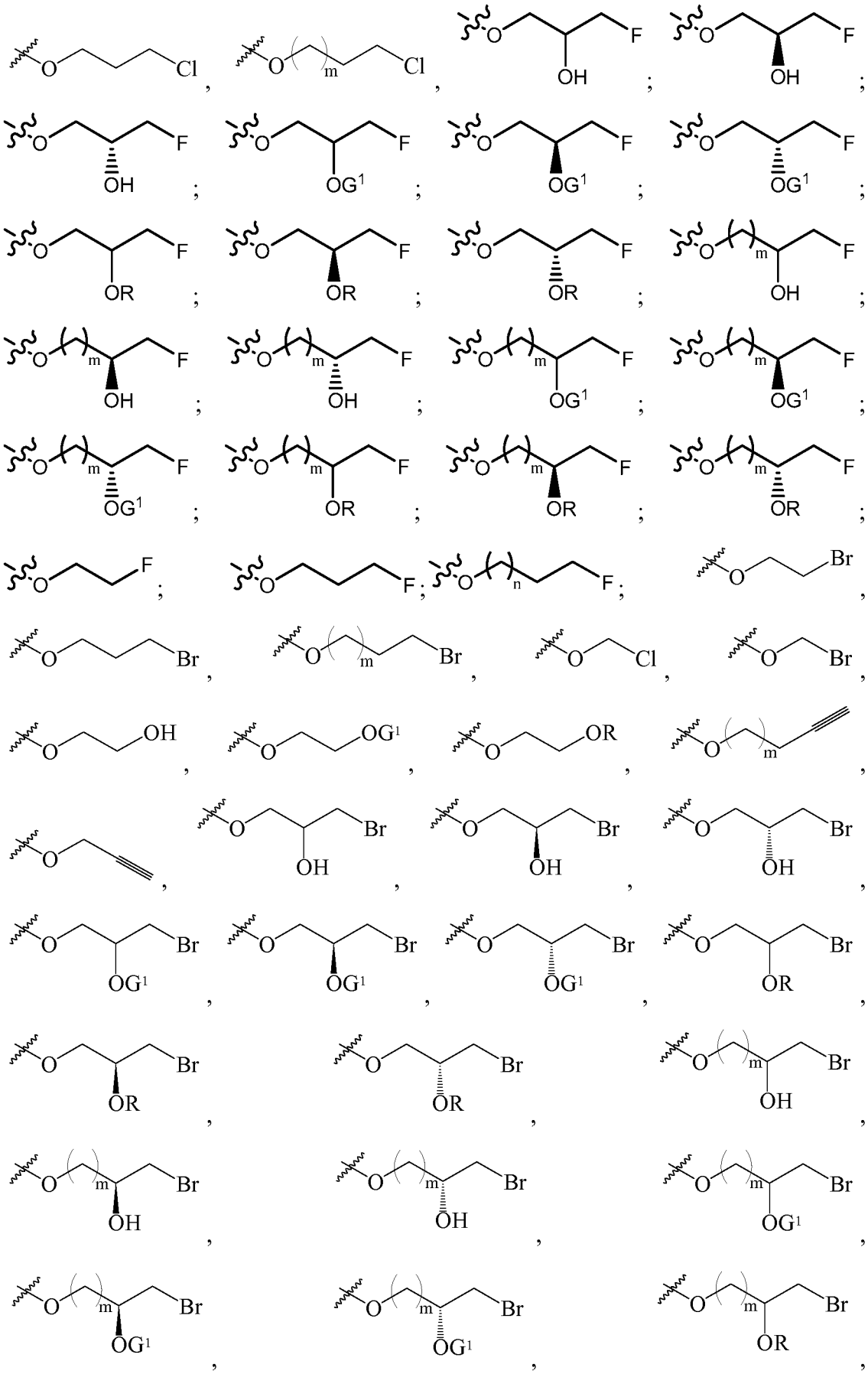

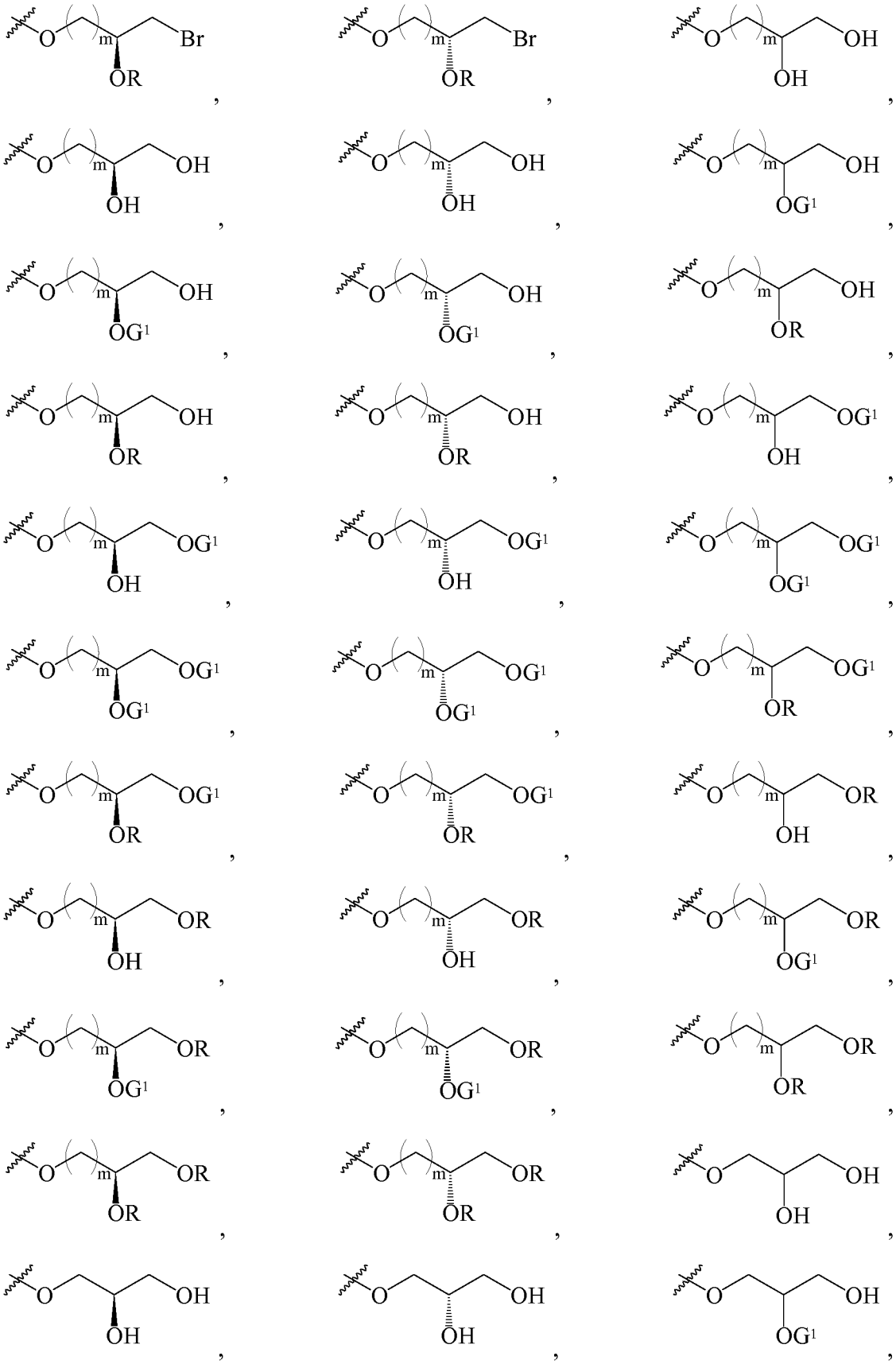

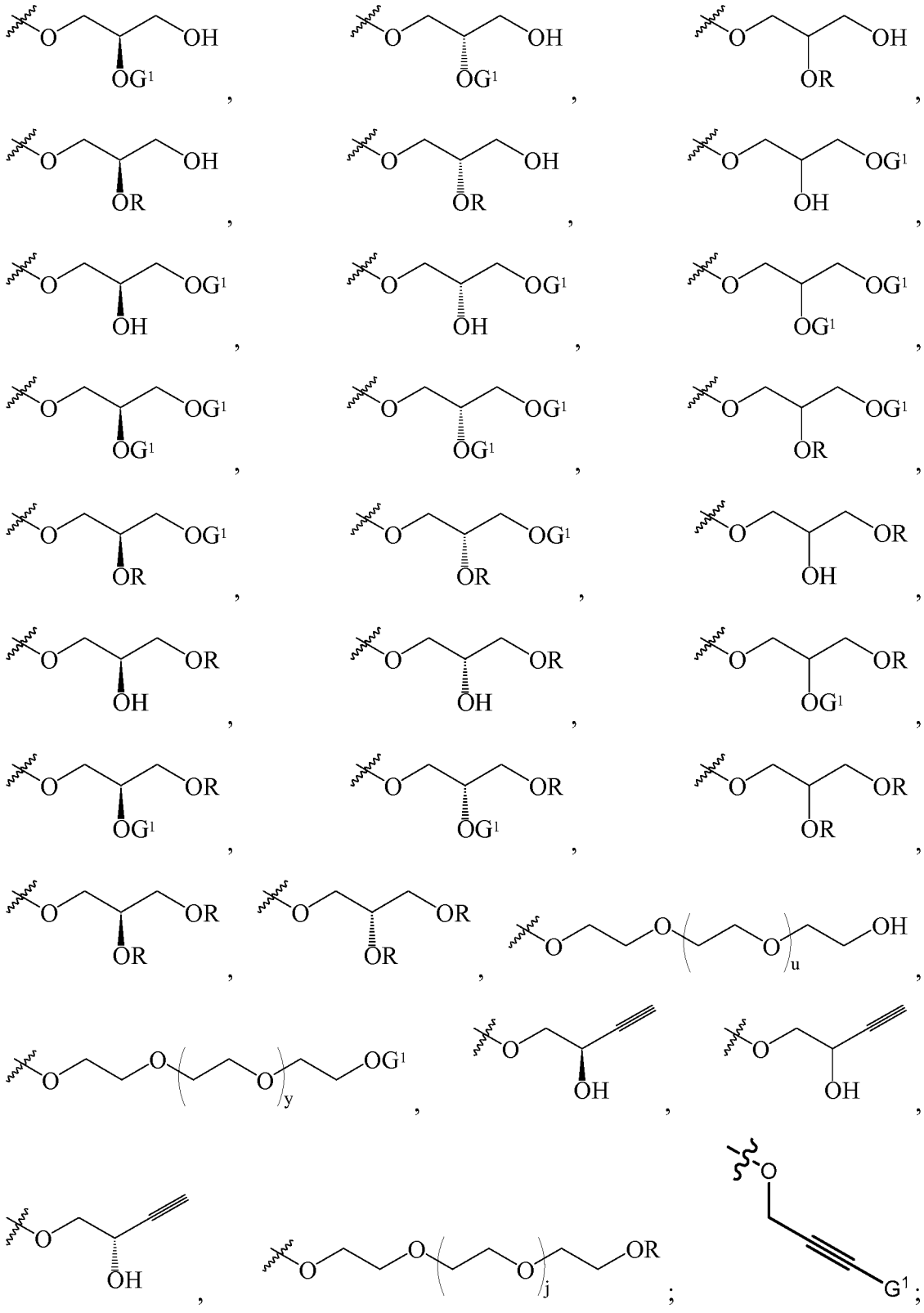

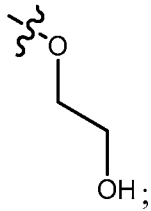
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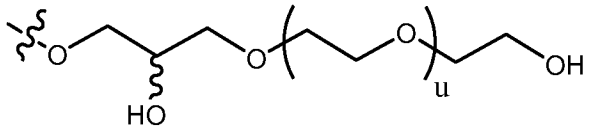
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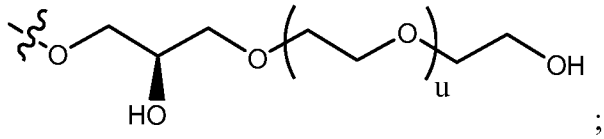
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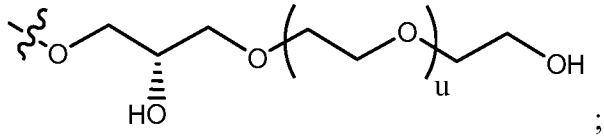
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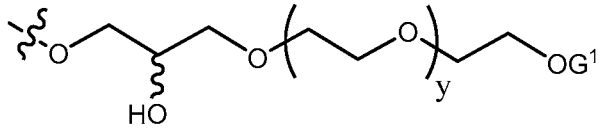
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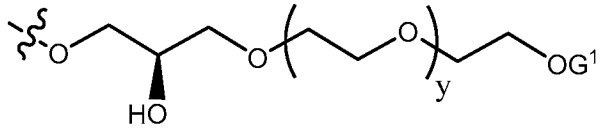
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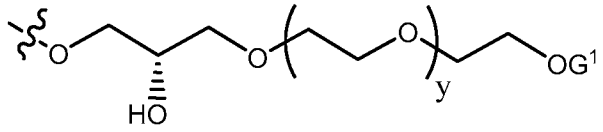
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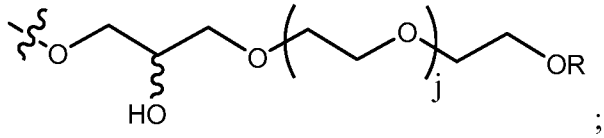
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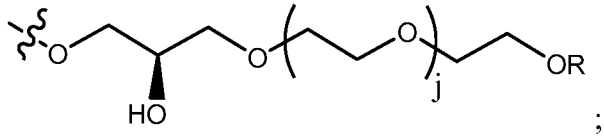
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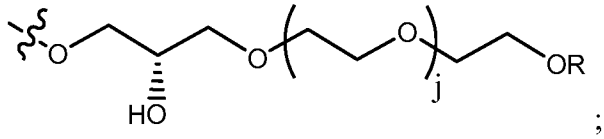
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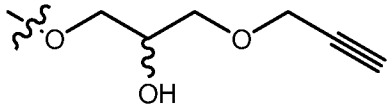
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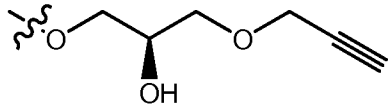
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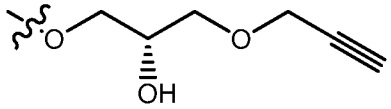
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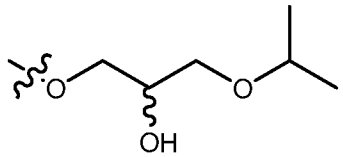
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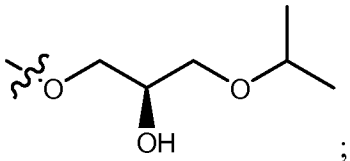
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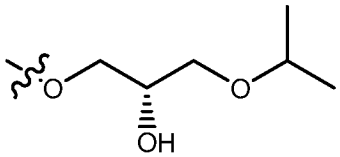
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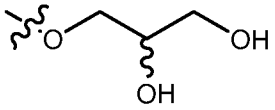
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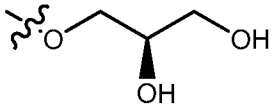
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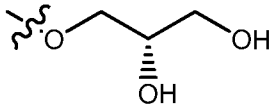
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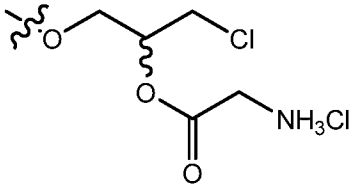
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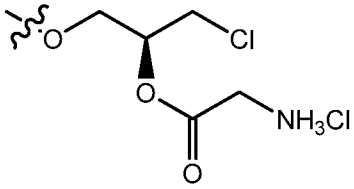
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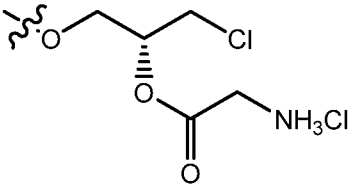
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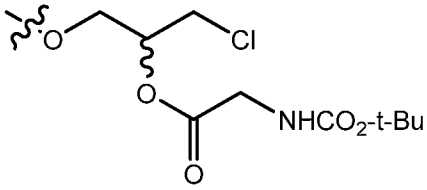
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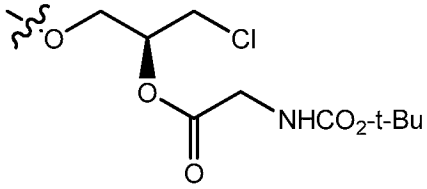
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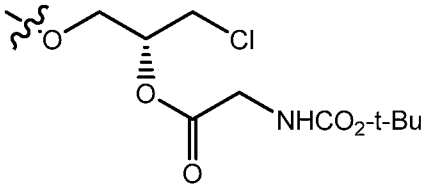
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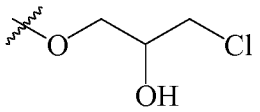
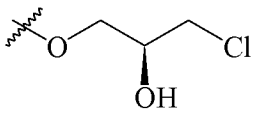
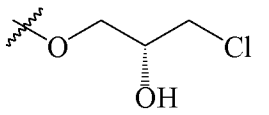
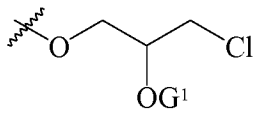
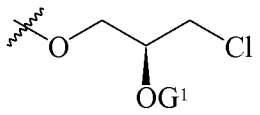
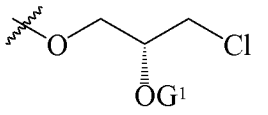
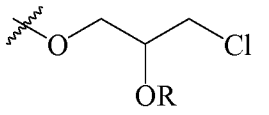
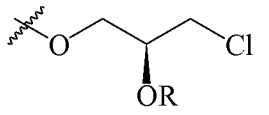
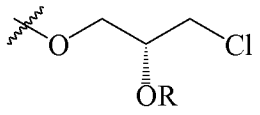
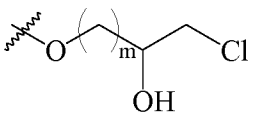
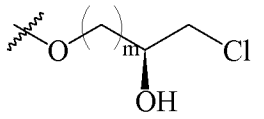
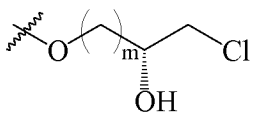
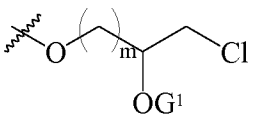
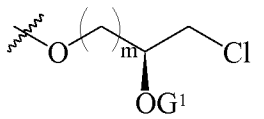
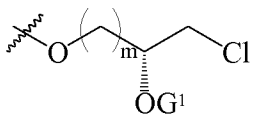
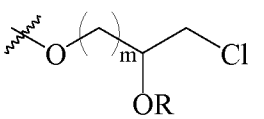
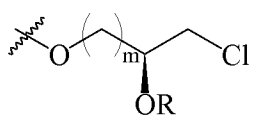
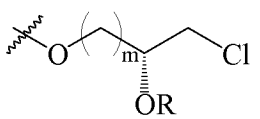
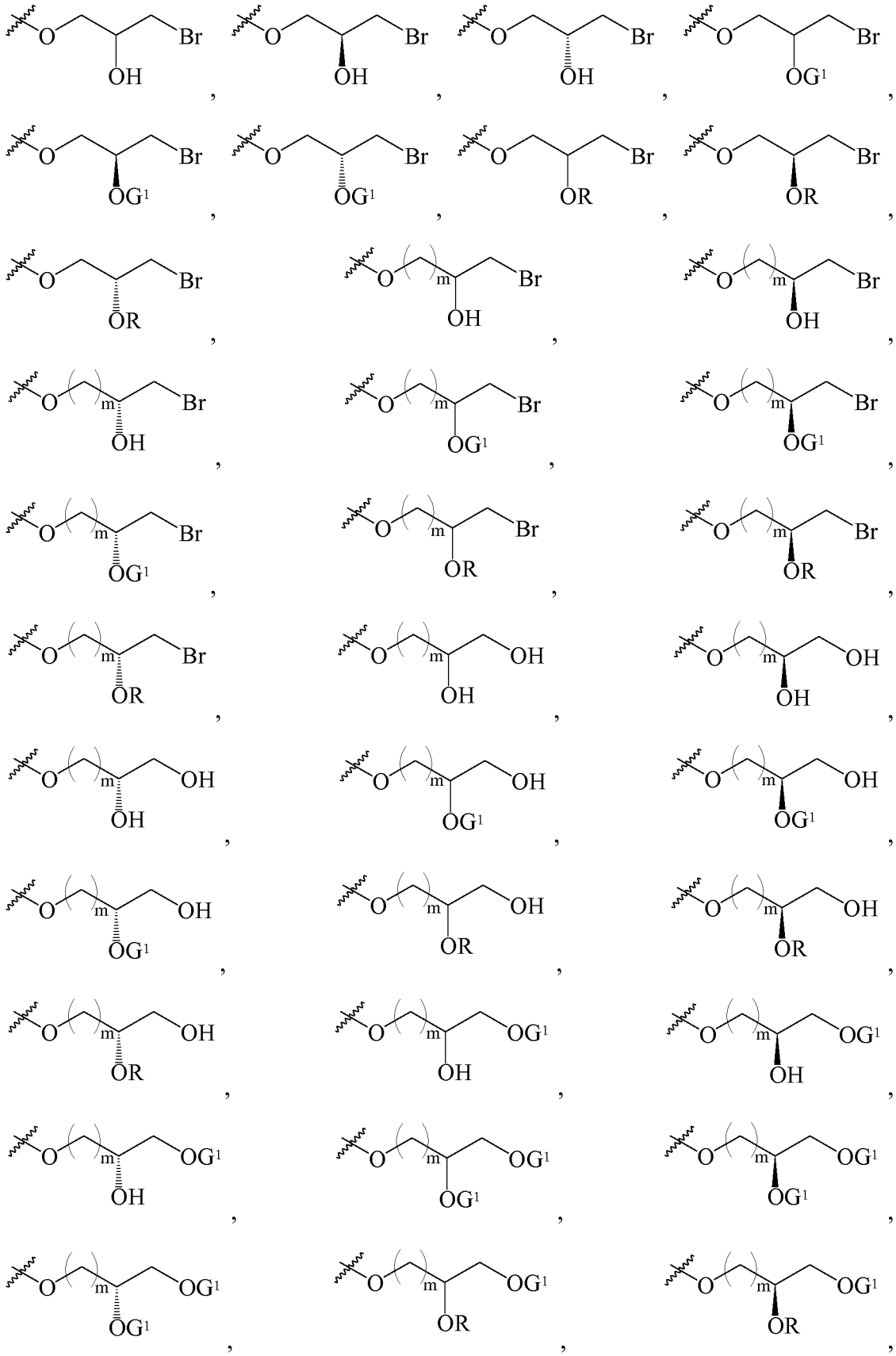
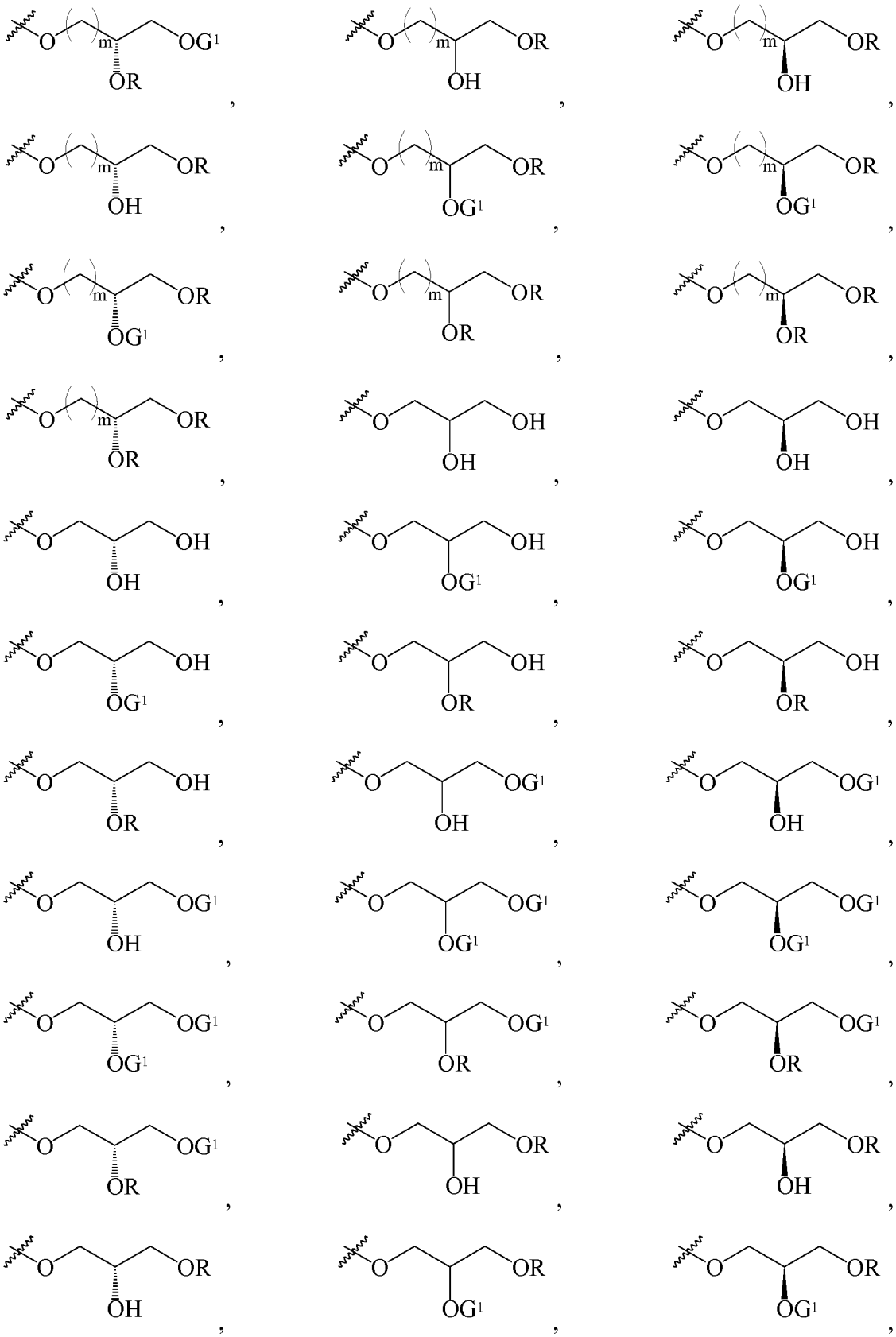
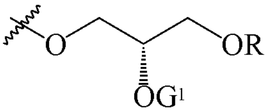
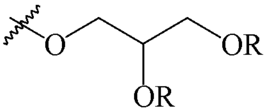
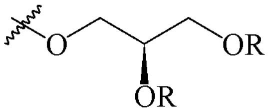
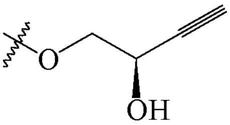
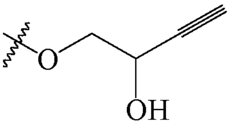
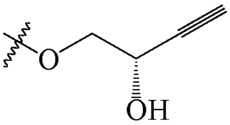
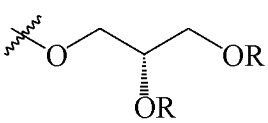
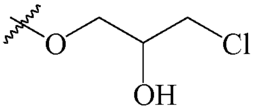
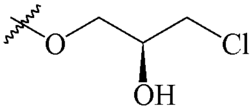
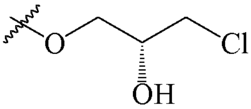
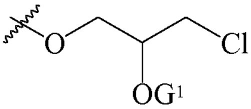
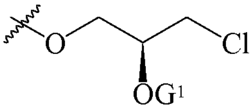
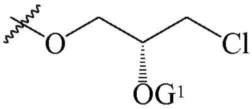
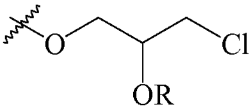
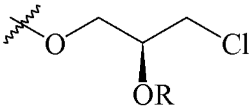
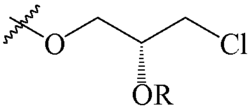
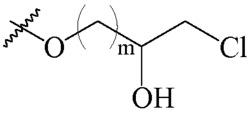
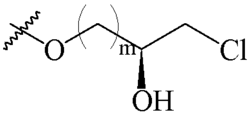
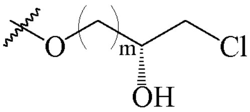
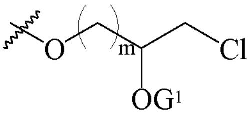
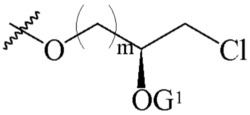
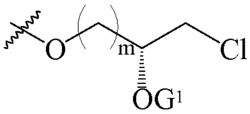
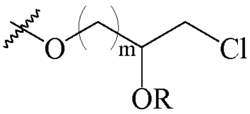
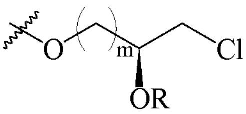
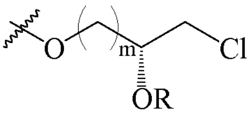
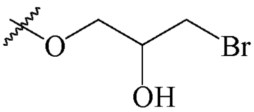
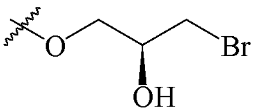
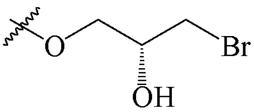
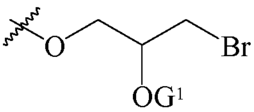
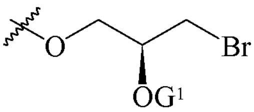
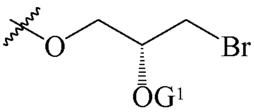
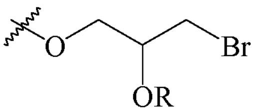
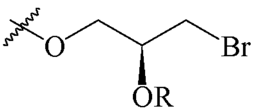
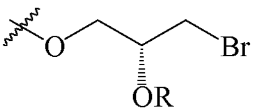
Each T may independently be  ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,





 ,  ,  ,

 ,  ,  , or  .

Each T may independently be  ,  ,  ,  ,  ,  ,  ,  , or  . Each T may independently be  ,  ,  ,  ,  ,  ,  ,  , or  . Each T may independently be  ,  ,  ,  ,  ,  ,  ,  , or  . 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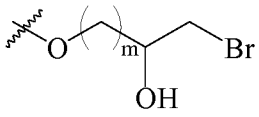
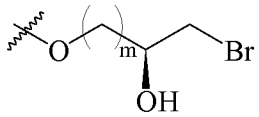
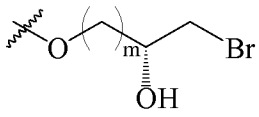
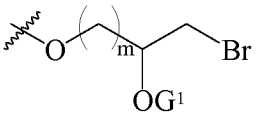
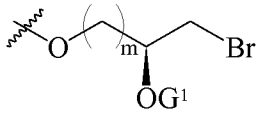
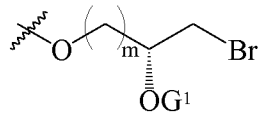
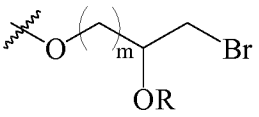
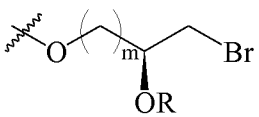
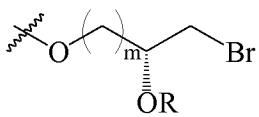

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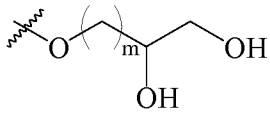
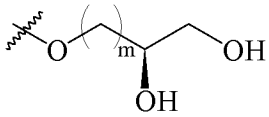
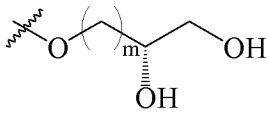
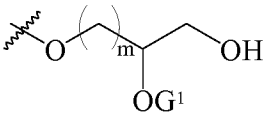
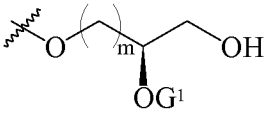
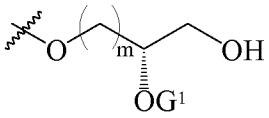
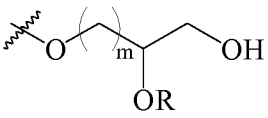
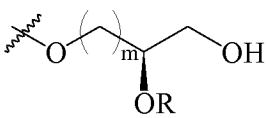
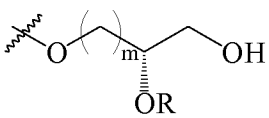

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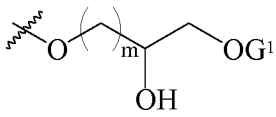
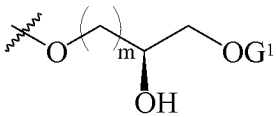
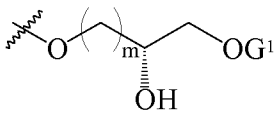
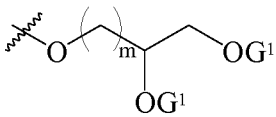
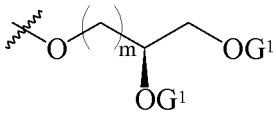
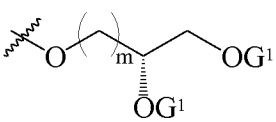
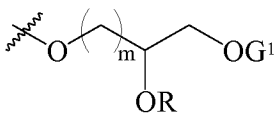
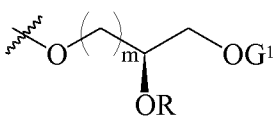
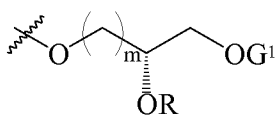
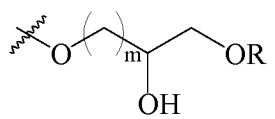

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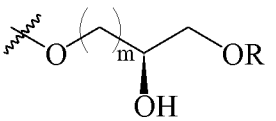
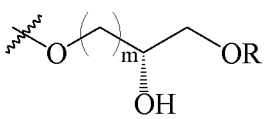
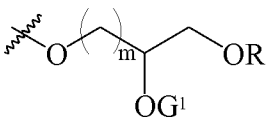

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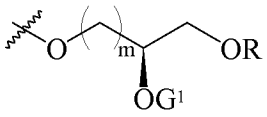
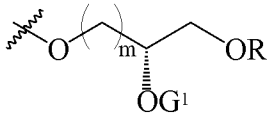
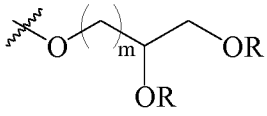
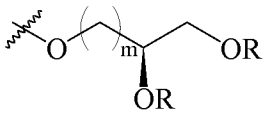
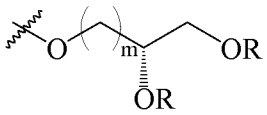

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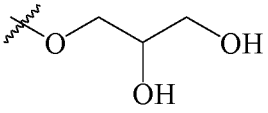
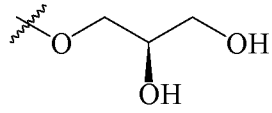
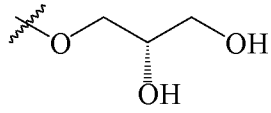
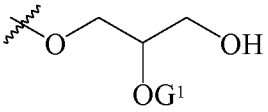
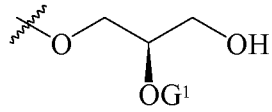
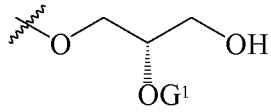
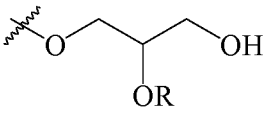
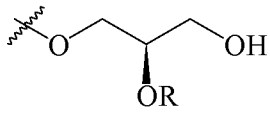
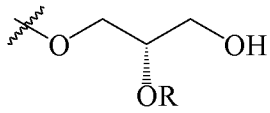

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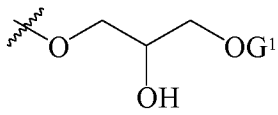
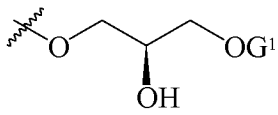
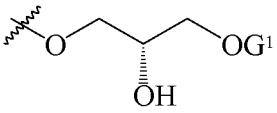
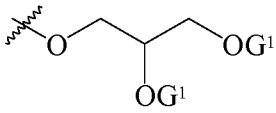
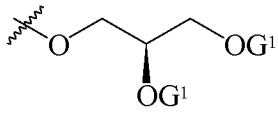
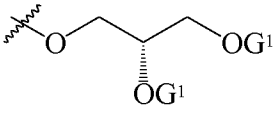
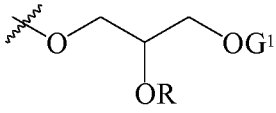
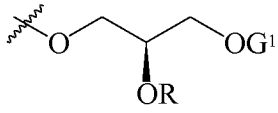
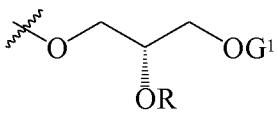
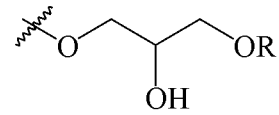

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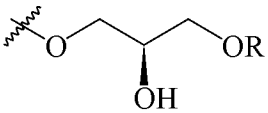
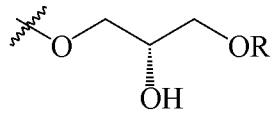
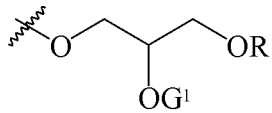
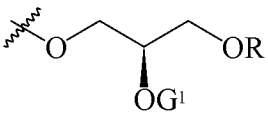
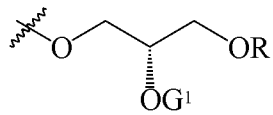
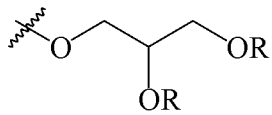

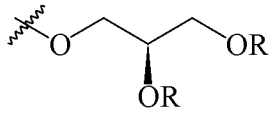
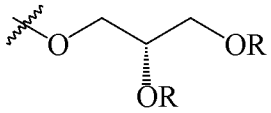

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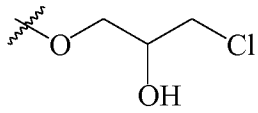
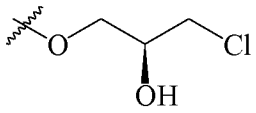
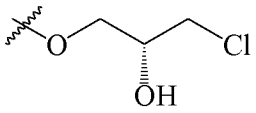

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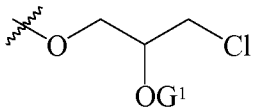
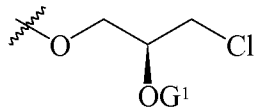
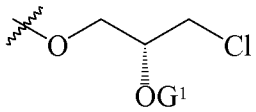

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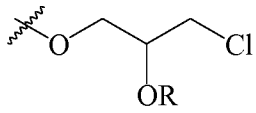
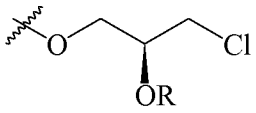

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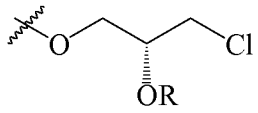
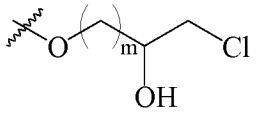

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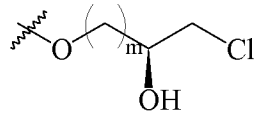
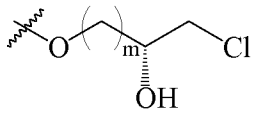

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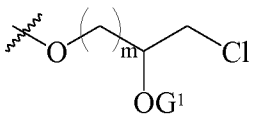
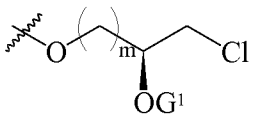
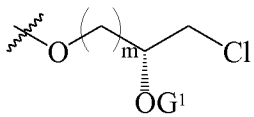

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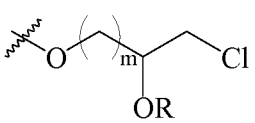
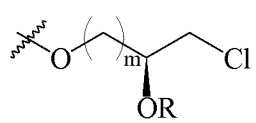
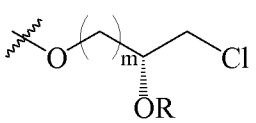

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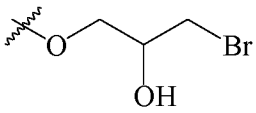
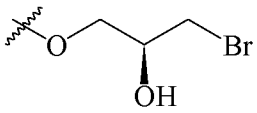

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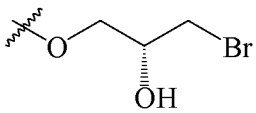
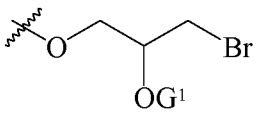

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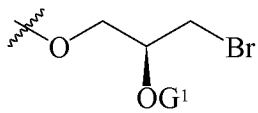
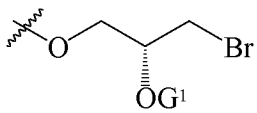

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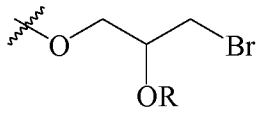
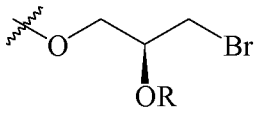
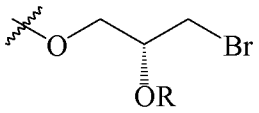

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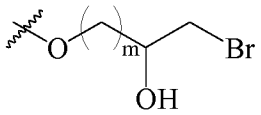
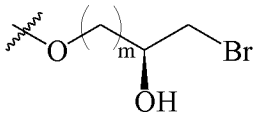
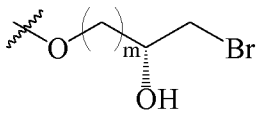

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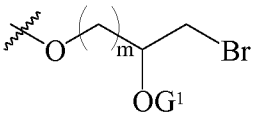
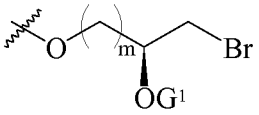

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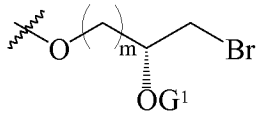
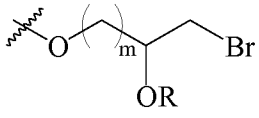

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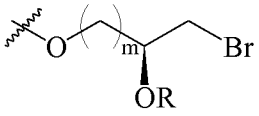
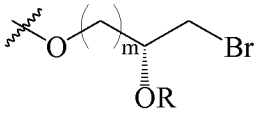

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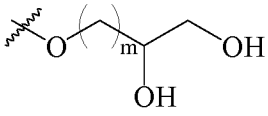
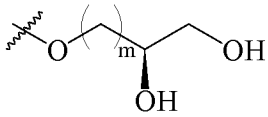
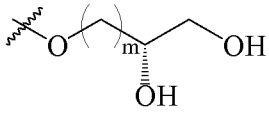

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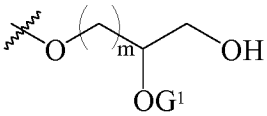
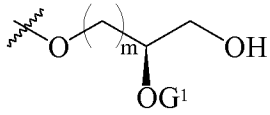

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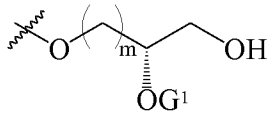
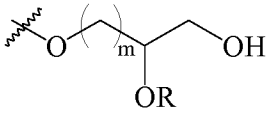

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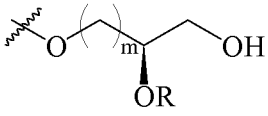
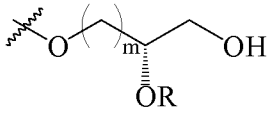

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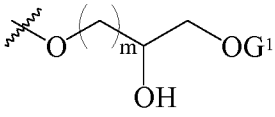
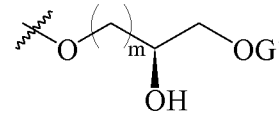
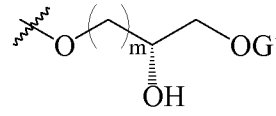

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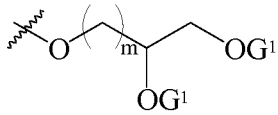
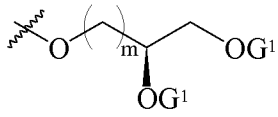

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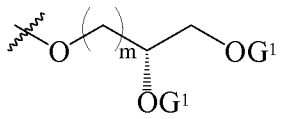
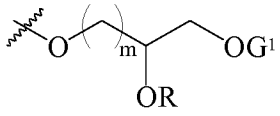

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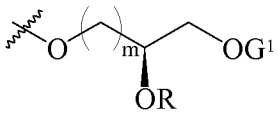
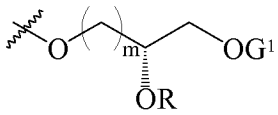

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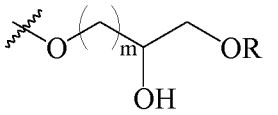
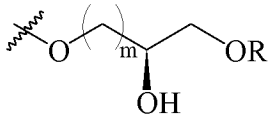
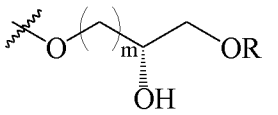

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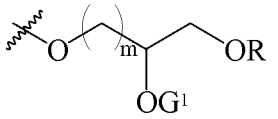
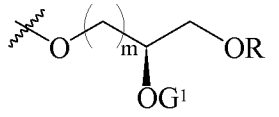

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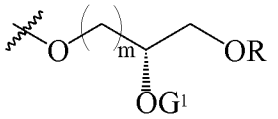
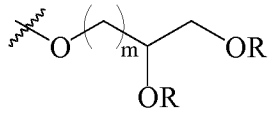

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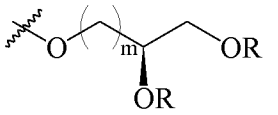
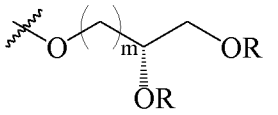

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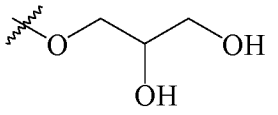
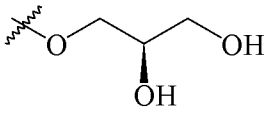
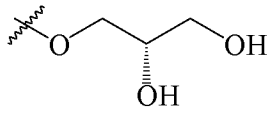

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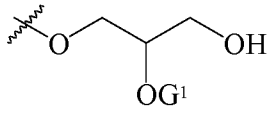
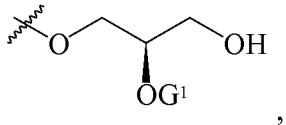

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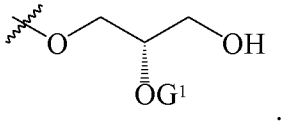
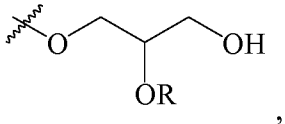

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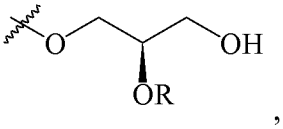
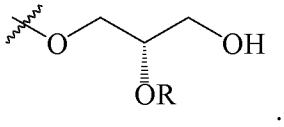

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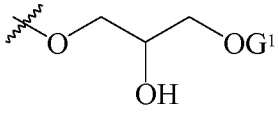
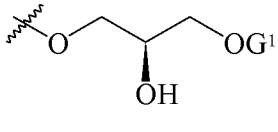
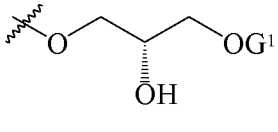

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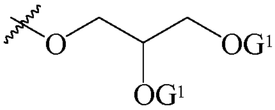
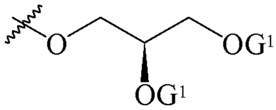
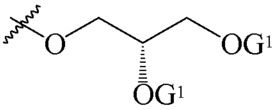
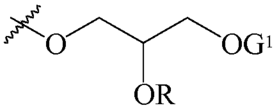
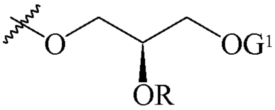
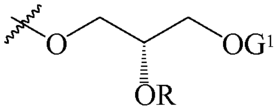
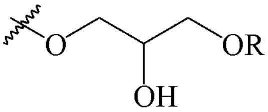
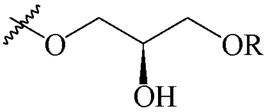
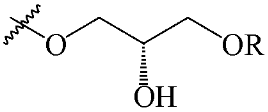
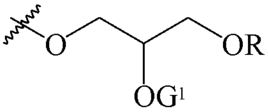
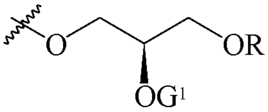
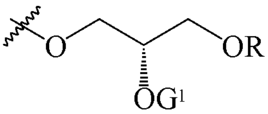
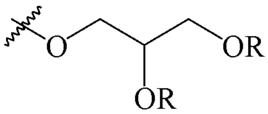
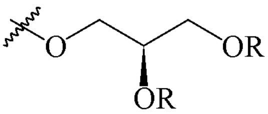
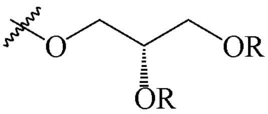
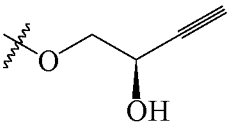
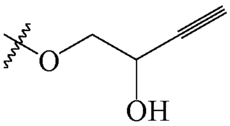
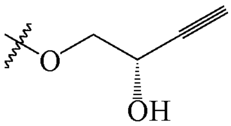
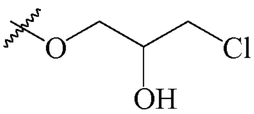
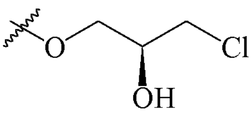
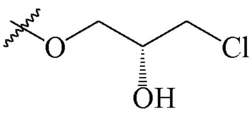
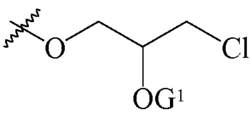
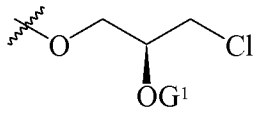
independently be  ,  , or  . Each T may independently be  ,  , or  . Each T may independently be  ,  , or  . Each T may independently be  ,  , or  . Each T may independently be  ,  , or  . Each T may independently be  ,  , or  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be



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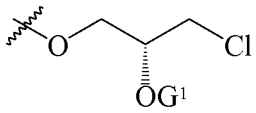

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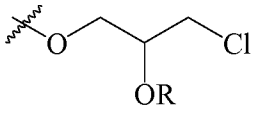

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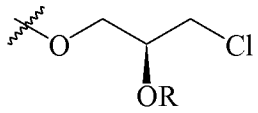

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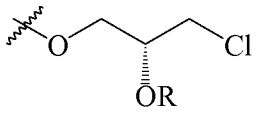

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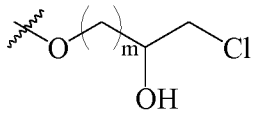

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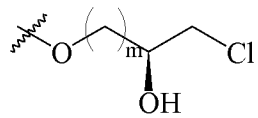

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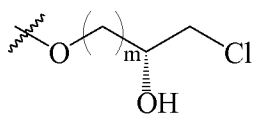

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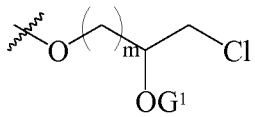

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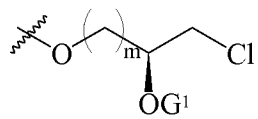

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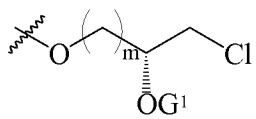

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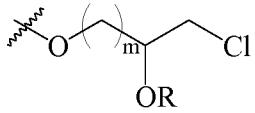

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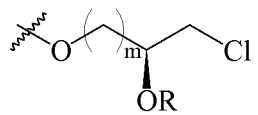

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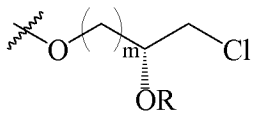

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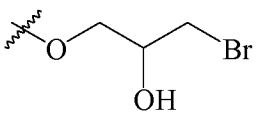

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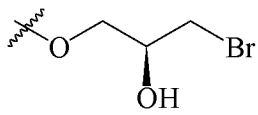

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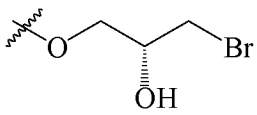

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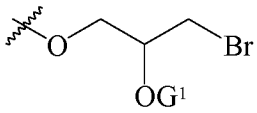
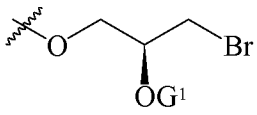
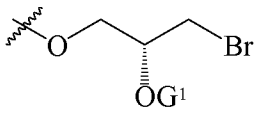
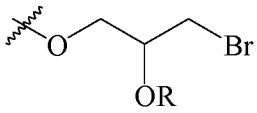
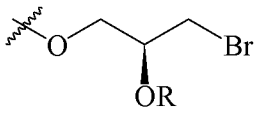
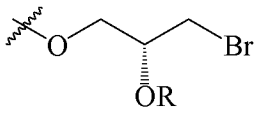
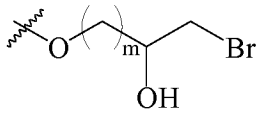
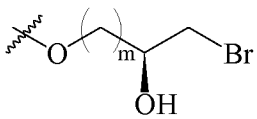
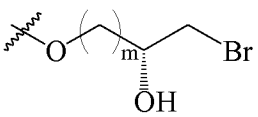
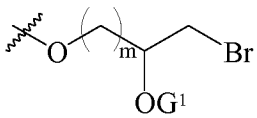
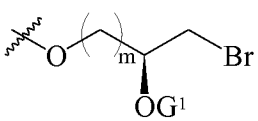
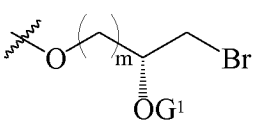
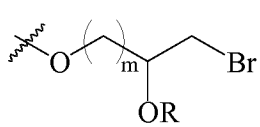
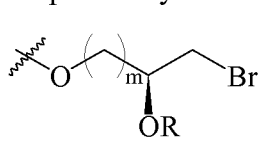
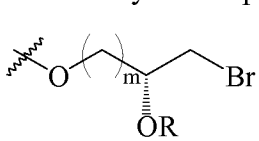
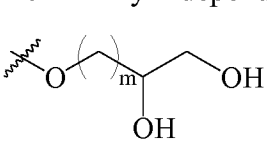
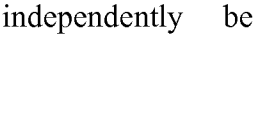
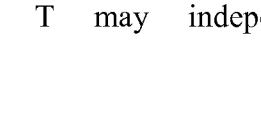
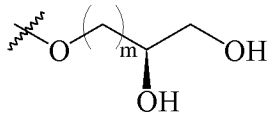
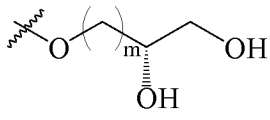
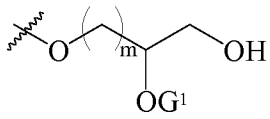
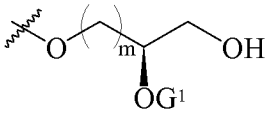
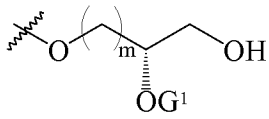
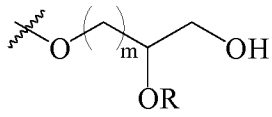
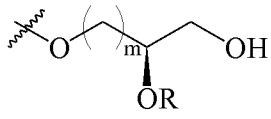
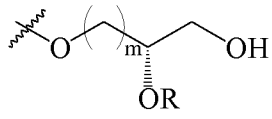
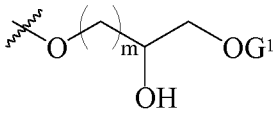
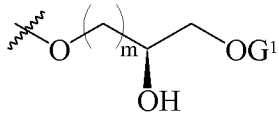
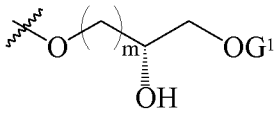
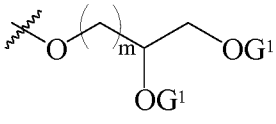
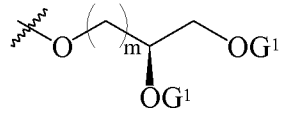
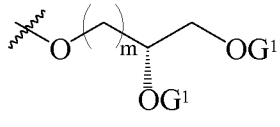
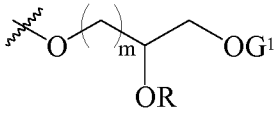
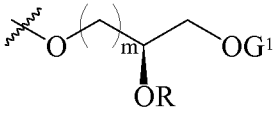
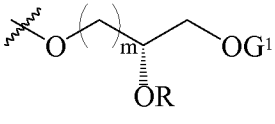
independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be . Each T may independently be


. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
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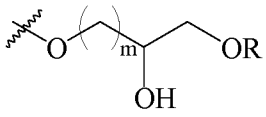
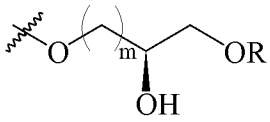
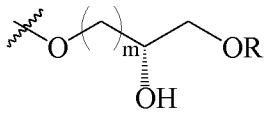
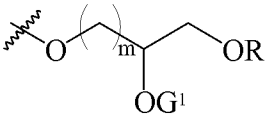
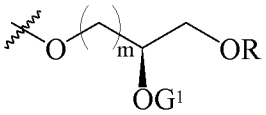
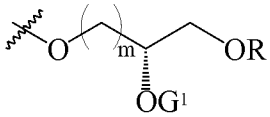
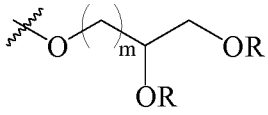
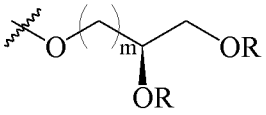
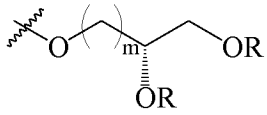
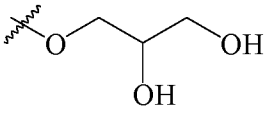
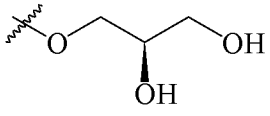
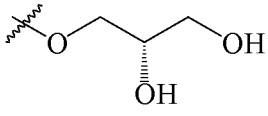
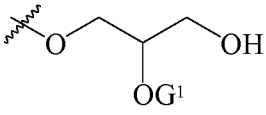
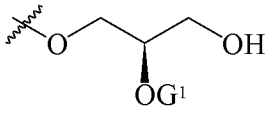
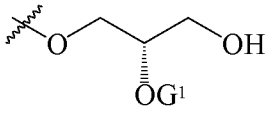
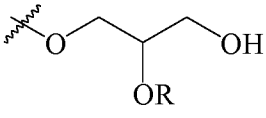
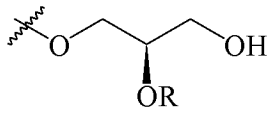
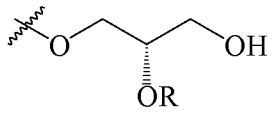
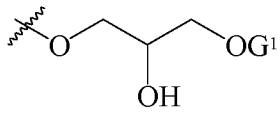
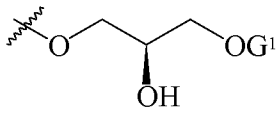
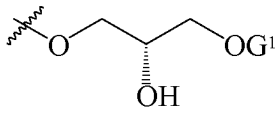
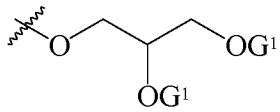
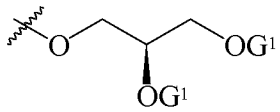
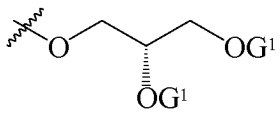
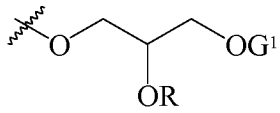
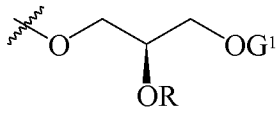
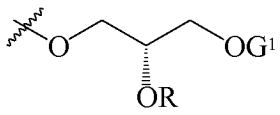
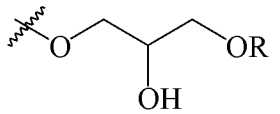
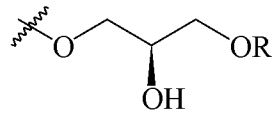
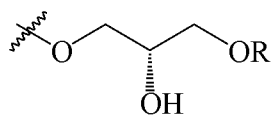
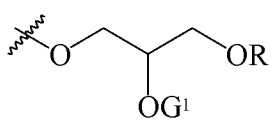
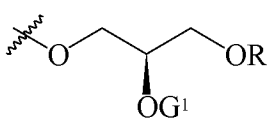
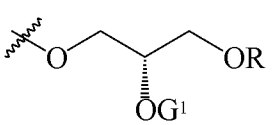
may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be . Each T may independently be . Each T may independently be


. Each T may independently be 
. 
.Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
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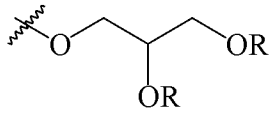
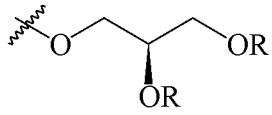
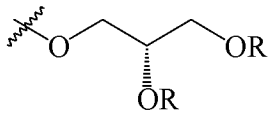
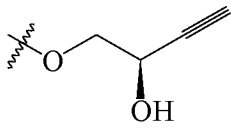
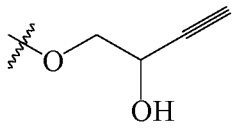
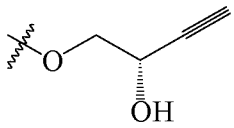
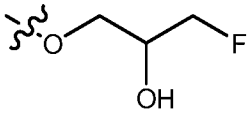
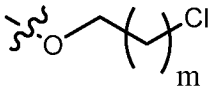
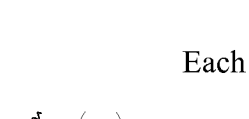
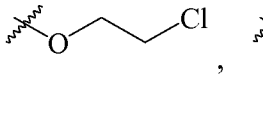
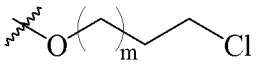
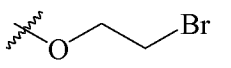
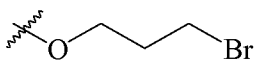
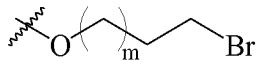
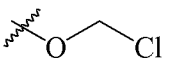
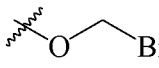
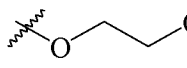
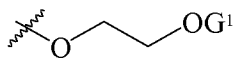
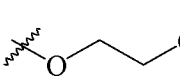

. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
. Each T may independently be 
, 
, 
, 
, 
, 
, 
, 
, 
, 
, 
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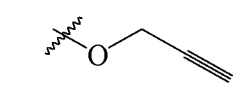
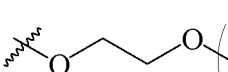
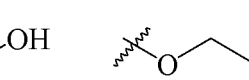
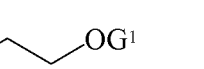
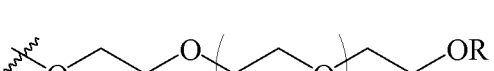
, 
, 
, 
, 
, 
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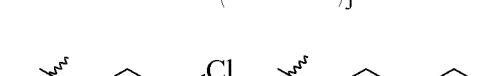
, or 
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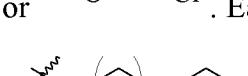
, or 
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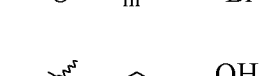
, 
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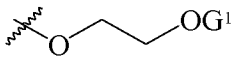
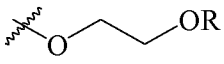
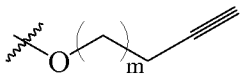
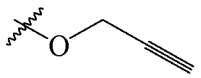
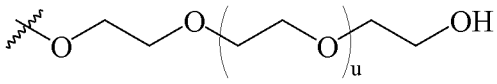
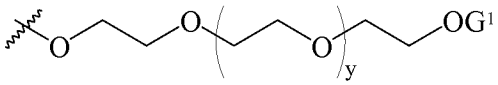
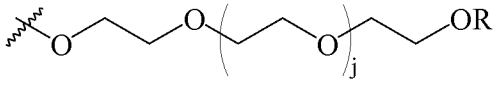
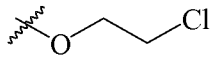
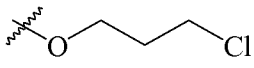
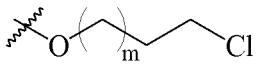
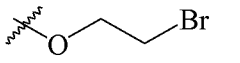
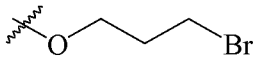
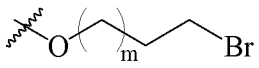
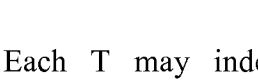
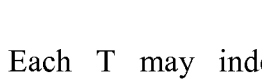
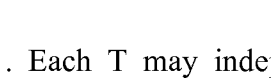
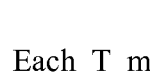
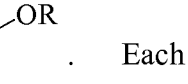
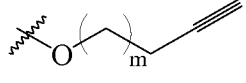
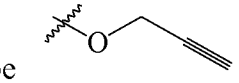
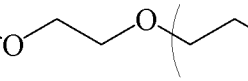
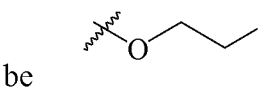
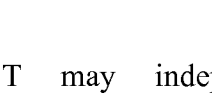
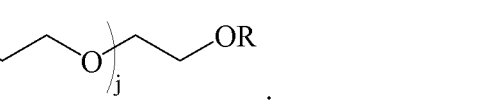
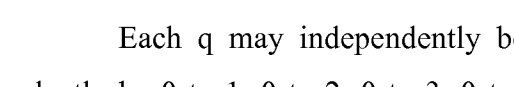
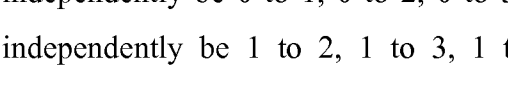
 , or  . Each T may independently be  , or  . Each T may independently be  ,  , or  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  . Each T may independently be  .

Each q may independently be 0, 1, 2, 3, 4, 5, 6 or 7. Each q may independently be 0 to 1, 0 to 2, 0 to 3, 0 to 4, 0 to 5, 0 to 6, or 0 to 7. Each q may independently be 1 to 2, 1 to 3, 1 to 4, 1 to 5, 1 to 6, or 1 to 7. Each q may

independently be 2 to 3, 2 to 4, 2 to 5, 2 to 6, or 2 to 7. Each q may independently be 3 to 4, 3 to 5, 3 to 6, or 3 to 7. Each q may be 0. Each q may be 1. Each q may be 2. Each q may be 3. Each q may be 4. Each q may be 5. Each q may be 6. Each q may be 7.

Each r may independently be 0, 1, 2, 3, 4, 5, 6 or 7. Each r may independently be 0 to 1, 0 to 2, 0 to 3, 0 to 4, 0 to 5, 0 to 6, 0 to 7. Each r may independently be 1 to 2, 1 to 3, 1 to 4, 1 to 5, 1 to 6, or 1 to 7. Each r may independently be 2 to 3, 2 to 4, 2 to 5, 2 to 6, or 2 to 7. Each r may independently be 3 to 4, 3 to 5, 3 to 6, or 3 to 7. Each r may be 0. Each r may be 1. Each r may be 2. Each r may be 3. Each r may be 4. Each r may be 5. Each r may be 6. Each r may be 7.

Each t may independently be 0, 1, 2, 3, 4, 5, 6 or 7. Each t may independently be 0 to 1, 0 to 2, 0 to 3, 0 to 4, 0 to 5, 0 to 6, or 0 to 7. Each t may independently be 1 to 2, 1 to 3, 1 to 4, 1 to 5, 1 to 6, or 1 to 7. Each t may independently be 2 to 3, 2 to 4, 2 to 5, 2 to 6, or 2 to 7. Each t may independently be 3 to 4, 3 to 5, 3 to 6, or 3 to 7. Each t may be 0. Each t may be 1. Each t may be 2. Each t may be 3. Each t may be 4. Each t may be 5. Each t may be 6. Each t may be 7.

Each n may independently be 0, 1, 2, 3, 4, 5, 6, 7 or 8. Each n may independently be 0 to 1, 0 to 2, 0 to 3, 0 to 4, 0 to 5, 0 to 6, 0 to 7, or 0 to 8. Each n may independently be 1 to 2, 1 to 3, 1 to 4, 1 to 5, 1 to 6, 1 to 7, or 1 to 8. Each n may independently be 2 to 3, 2 to 4, 2 to 5, 2 to 6, 2 to 7, or 2 to 8. Each n may independently be 3 to 4, 3 to 5, 3 to 6, 3 to 7, or 3 to 8. Each n may be 0. Each n may be 1. Each n may be 2. Each n may be 3. Each n may be 4. Each n may be 5. Each n may be 6. Each n may be 7. Each n may be 8.

Each u may independently be 0, 1, 2, 3, 4, 5, 6 or 7. Each u may independently be 0 to 1, 0 to 2, 0 to 3, 0 to 4, 0 to 5, 0 to 6, 0 to 7. Each u may independently be 1 to 2, 1 to 3, 1 to 4, 1 to 5, 1 to 6, or 1 to 7. Each u may independently be 2 to 3, 2 to 4, 2 to 5, 2 to 6, or 2 to 7. Each u may independently be 3 to 4, 3 to 5, 3 to 6, or 3 to 7. Each u may be 0. Each u may be 1. Each u may be 2. Each u may be 3. Each u may be 4. Each u may be 5. Each u may be 6. Each u may be 7.

Each y may independently be 0, 1, 2, 3, 4, 5, 6 or 7. Each y may independently be 0 to 1, 0 to 2, 0 to 3, 0 to 4, 0 to 5, 0 to 6, or 0 to 7. Each y may independently be 1 to 2, 1 to 3, 1 to 4, 1 to 5, 1 to 6, or 1 to 7. Each y may independently be 2 to 3, 2 to 4, 2 to 5, 2 to 6, or 2 to 7. Each y may independently be 3

to 4, 3 to 5, 3 to 6, or 3 to 7. Each y may be 0. Each y may be 1. Each y may be 2. Each y may be 3. Each y may be 4. Each y may be 5. Each y may be 6. Each y may be 7.

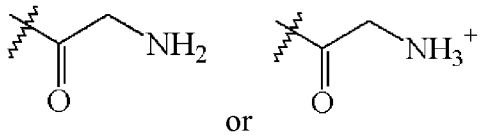
Each j may independently be 0, 1, 2, 3, 4, 5, 6 or 7. Each j may independently be 0 to 1, 0 to 2, 0 to 3, 0 to 4, 0 to 5, 0 to 6, or 0 to 7. Each j may independently be 1 to 2, 1 to 3, 1 to 4, 1 to 5, 1 to 6, or 1 to 7. Each j may independently be 2 to 3, 2 to 4, 2 to 5, 2 to 6, or 2 to 7. Each j may independently be 3 to 4, 3 to 5, 3 to 6, or 3 to 7. Each j may be 0. Each j may be 1. Each j may be 2. Each j may be 3. Each j may be 4. Each j may be 5. Each j may be 6. Each j may be 7.

Each m may independently be 0, 1, 2, 3, 4, 5, 6, 7 or 8. Each m may independently be 0 to 1, 0 to 2, 0 to 3, 0 to 4, 0 to 5, 0 to 6, 0 to 7, or 0 to 8. Each m may independently be 1 to 2, 1 to 3, 1 to 4, 1 to 5, 1 to 6, 1 to 7, or 1 to 8. Each m may independently be 2 to 3, 2 to 4, 2 to 5, 2 to 6, 2 to 7, or 2 to 8. Each m may independently be 3 to 4, 3 to 5, 3 to 6, 3 to 7, or 3 to 8. Each m may be 0. Each m may be 1. Each m may be 2. Each m may be 3. Each m may be 4. Each m may be 5. Each m may be 6. Each m may be 7. Each m may be 8.

At least one Z^1 is C-Q, at least one Z^2 is C-W, at least one Z^3 is C-T, CH, CCH_3, CF, CCl, CBr, CI, COH, CG^1, COG^1, CNH_2, $CNHG^1$, $CNG^1{}_2$, $COSO_3H$, $COPO_3H_2$, CSG^1, $CSOG^1$, or CSO_2G^1, and each remaining Z^1, Z^2 and Z^3 is, at each occurrence, independently C-T, N, CH, CCH_3, CF, CCl, CBr, CI, COH, CG^1, COG^1, CNH_2, $CNHG^1$, $CNG^1{}_2$, $COSO_3H$, $COPO_3H_2$, CSG^1, $CSOG^1$, or CSO_2G^1 or at least one Z^3 may independently be C-T, and each remaining Z^1, Z^2 and Z^3 may, at each occurrence, independently be N, CH, CF, CCl, CBr, CI, CG^1, or COH. At least one Z^1 may independently be C-Q, at least one Z^2 or Z^3 may independently be COH, and each remaining Z^1, Z^2 and Z^3 may, at each occurrence, independently be N, CH, CF, CCl, CBr, CI, CG^1, or COH. At least one Z^1 may, at each occurrence, independently be C-Q, at least one Z^2 or Z^3 may, at each occurrence, independently be C-T, and each remaining Z^1, Z^2 and Z^3 may, at each occurrence, independently be N, CH, CF, CCl, CBr, CI, or COH. At least one Z^1 may independently be C-Q, at least one Z^2 or Z^3 may independently be COH, and each remaining Z^1, Z^2 and Z^3 may, at each occurrence, independently be N, CH, CF, CCl, CBr, CI, or COH. At least one Z^1 may independently be C-Q, at least one Z^2 or Z^3 may independently be C-T, and each remaining Z^1, Z^2 and Z^3 may, at each occurrence, independently be CH. At least one Z^1 may independently be C-Q, at least one Z^2 or Z^3 may independently be COH, and each remaining Z^1, Z^2 and

Z^3 may, at each occurrence, independently be CH. In any of the foregoing embodiments, each remaining Z^1, Z^2 and Z^3 may, at each occurrence, independently be N, CH, CF, CCl, CBr, CI, COH, CCH_3, CNH_2, $COSO_3H$, or $COPO_3H_2$, each remaining Z^1, Z^2 and Z^3 may, at each occurrence, independently be N, CH, CF, CCl, CBr, CI, COH, CNH_2, $COSO_3H$, or $COPO_3H_2$, each remaining Z^1, Z^2 and Z^3 may, at each occurrence, independently be N, CH, CF, CCl, CBr, CI, or COH, each remaining Z^1, Z^2 and Z^3 may, at each occurrence, independently be CH, CF, CCl, CBr, or CI, each remaining Z^1, Z^2 and Z^3 may, at each occurrence, independently be CH, CCl, or CBr or each remaining Z^1, Z^2 and Z^3 may, at each occurrence, be CH.

Each of J″ and J‴ may independently be a moiety selected from TABLE 1. Each of J″, and J‴ may independently be an amino acid based moiety or a polyethylene glycol based moiety selected from TABLE 1. Alternatively, each of J″, and J‴ may independently an amino acid based moiety selected from TABLE 1. Each J″, and J‴ may be



or .

Each G^1 $G^{1\prime}$ and $G^{1\prime\prime}$ may independently be linear or branched, or aromatic cyclic or non-aromatic cyclic, substituted or unsubstituted, saturated or unsaturated C_1-C_{10} alkyl. Each G^1, $G^{1\prime}$ and $G^{1\prime\prime}$ may independently be a branched, linear, or non-aromatic cyclic, substituted or unsubstituted, saturated or unsaturated C_1-C_{10} alkyl. Each G^1, $G^{1\prime}$ and $G^{1\prime\prime}$ may independently be a branched, linear, or non-aromatic cyclic, substituted or saturated or unsaturated C_1-C_{10} alkyl. Each G^1, $G^{1\prime}$ and $G^{1\prime\prime}$ may independently be a branched, unbranched, or aromatic cyclic or non-aromatic cyclic, substituted or unsubstituted, saturated or unsaturated C_1-C_9 alkyl. Each G^1, $G^{1\prime}$ and $G^{1\prime\prime}$ may independently be a branched, unbranched, or aromatic cyclic or non-aromatic cyclic, substituted or unsubstituted, saturated or unsaturated C_1-C_8 alkyl. Each G^1, $G^{1\prime}$ and $G^{1\prime\prime}$ may independently be a branched, unbranched, or aromatic cyclic or non-aromatic cyclic, substituted or unsubstituted, saturated or unsaturated C_1-C_7 alkyl. Each G^1, $G^{1\prime}$ and $G^{1\prime\prime}$ may independently be a branched, unbranched, or aromatic cyclic or non-aromatic cyclic, substituted or unsubstituted, saturated or unsaturated C_1-C_6

alkyl. Each G^1, $G^{1\prime}$ and $G^{1\prime\prime}$ may independently be a branched, unbranched, or aromatic cyclic or non-aromatic cyclic, substituted or unsubstituted, saturated or unsaturated C_1-C_5 alkyl. Each G^1, $G^{1\prime}$ and $G^{1\prime\prime}$ may independently be a branched, unbranched, or non-aromatic cyclic, substituted or unsubstituted, saturated or unsaturated C_1-C_4 alkyl. Each G^1, $G^{1\prime}$ and $G^{1\prime\prime}$ may independently be a branched, unbranched, or non-aromatic cyclic, substituted or unsubstituted, saturated or unsaturated C_1-C_3 alkyl. Each G^1, $G^{1\prime}$ and $G^{1\prime\prime}$ may independently be a substituted or unsubstituted, saturated or unsaturated C_1-C_2 alkyl.

Each G^1 may independently be a non-aromatic cyclic, substituted or unsubstituted, saturated or unsaturated cyclopropyl. Each G^1 may independently be a non-aromatic cyclic, substituted or unsubstituted, saturated or unsaturated cyclobutyl. Each G^1 may independently be an aromatic cyclic or non-aromatic cyclic, substituted or unsubstituted, saturated or unsaturated cyclobutyl. Each G^1 may independently be an aromatic cyclic or non-aromatic cyclic, substituted or unsubstituted, saturated or unsaturated cyclopentyl. Each G^1 may independently be an aromatic cyclic or non-aromatic cyclic, substituted or unsubstituted, saturated or unsaturated cyclohexyl. Each G^1 may independently be an aromatic cyclic or non-aromatic cyclic, substituted or unsubstituted, saturated or unsaturated cycloheptyl. Each G^1 may independently be an aromatic cyclic or non-aromatic cyclic, substituted or unsubstituted, saturated or unsaturated cyclooctyl. Each G^1 may independently be cyclohexyl.

Each G^1 may independently be substituted or unsubstituted methyl. Each G^1 may independently be substituted or unsubstituted, saturated or unsaturated ethyl. Each G^1 may independently be a branched, unbranched, substituted or unsubstituted, saturated or unsaturated propyl. Each G^1 may be isopropyl. Each G^1 may independently be a branched, unbranched, substituted or unsubstituted, saturated or unsaturated butyl. Each G^1 may be n-butyl. Each G^1 may independently be a branched, unbranched, substituted or unsubstituted, saturated or unsaturated pentyl. Each G^1 may independently be a branched, unbranched, substituted or unsubstituted, saturated or unsaturated hexyl. Each G^1 may independently be a branched, unbranched, substituted or unsubstituted, saturated or unsaturated heptyl. Each G^1 may independently be a

branched, unbranched, substituted or unsubstituted, saturated or unsaturated octyl. Each G^1 may be propargyl ($CH_2C{\equiv}CH$).

An optional substituent may be selected from the group consisting of oxo, OJ′″, COOH, R^4, OH, OR^4, F, Cl, Br, I, NH_2, NHR^4, $NR^4{}_2$, CN, SH, SR^4, SO_3H, SO_3R^4, SO_2R^4, OSO_3R^4, OR^5, CO_2R^4, $CONH_2$, $CONHR^4$, $CONHR^5$, $CONR^4{}_2$, NHR^5, OPO_3H_3, $CONR^4R^5$, NR^4R^5, and NO_2. An optional substituent may be selected from the group consisting of: oxo (i.e. =O), OJ′″, COOH, R^4, OH, OR^4, F, Cl, Br, I, NH_2, NHR^4, $NR^4{}_2$, CN, SH, SR^4, SO_3H, SO_3R^4, SO_2R^4, OSO_3R^4, and NO_2. An optional substituent may be selected from the group consisting of: oxo (i.e. =O), OJ′″, COOH, R^4, OH, OR^4, F, Cl, Br, I, NH_2, NHR^4, $NR^4{}_2$, SO_3H, SO_3R^4, SO_2R^4, and NO_2. An optional substituent may be selected from the group consisting of: oxo (i.e. =O), OJ′″, COOH, R^4, OH, OR^4, F, Cl, Br, I, NH_2, and NO_2. An optional substituent may be selected from the group consisting of: oxo (i.e. =O), OJ′″, COOH, R^4, OH, OR^4, F, Cl, Br, and I. An optional substituent may be selected from the group consisting of: oxo (i.e. =O), OJ′″, COOH, OH, F, Cl, Br, and I. An optional substituent may be selected from the group consisting of: oxo (i.e. =O), OJ′″, COOH, OH, F, and Cl. Each linear or branched, or aromatic cyclic or non-aromatic cyclic, saturated or unsaturated C_1-C_{10} alkyl may be substituted with, for example, 1, 2, 3, 4, 5, or 6 substituents.

Each R′ may independently be a non-aromatic cyclic, substituted or unsubstituted, saturated or unsaturated cyclopropyl. Each R′ may independently be a non-aromatic cyclic, substituted or unsubstituted, saturated or unsaturated cyclobutyl. Each R′ may independently be an aromatic cyclic or non-aromatic cyclic, substituted or unsubstituted, saturated or unsaturated cyclobutyl. Each R′ may independently be an aromatic cyclic or non-aromatic cyclic, substituted or unsubstituted, saturated or unsaturated cyclopentyl. Each R′ may independently be an aromatic cyclic or non-aromatic cyclic, substituted or unsubstituted, saturated or unsaturated cyclohexyl. Each R′ may independently be an aromatic cyclic or non-aromatic cyclic, substituted or unsubstituted, saturated or unsaturated cycloheptyl. Each R′ may independently be an aromatic cyclic or non-aromatic cyclic, substituted or unsubstituted, saturated or unsaturated cyclooctyl.

Each R' may independently be substituted or unsubstituted methyl. Each R' may independently be substituted or unsubstituted, saturated or unsaturated ethyl. Each R' may independently be a branched, unbranched, substituted or unsubstituted, saturated or unsaturated propyl. Each R' may be isopropyl. Each R' may independently be a branched, unbranched, substituted or unsubstituted, saturated or unsaturated butyl. Each R' may be n-butyl. Each R' may independently be a branched, unbranched, substituted or unsubstituted, saturated or unsaturated pentyl. Each R' may independently be a branched, unbranched, substituted or unsubstituted, saturated or unsaturated hexyl. Each R' may independently be a branched, unbranched, substituted or unsubstituted, saturated or unsaturated heptyl. Each R' may independently be a branched, unbranched, substituted or unsubstituted, saturated or unsaturated octyl.

Each R' may independently be H. Each R' may independently be Li. Each R' may independently be Na. Each R' may independently be K. Each R' may independently be Mg. Each R' may independently be Ca.

Each R may independently be C_1-C_{10} acyl. Each R may independently be C_1-C_9 acyl. Each R may independently be C_1-C_8 acyl. Each R may independently be C_1-C_7 acyl. Each R may independently be C_1-C_6 acyl. Each R may independently be C_1-C_5 acyl. Each R may independently be C_1-C_4 acyl. Each R may independently be C_1-C_3 acyl. Each R may independently be C_1-C_2 acyl. Each R may independently be C_1 acyl. Each R may independently be C_2 acyl. Each R may independently be C_3 acyl. Each R may independently be C_4 acyl. Each R may independently be C_5 acyl. Each R may independently be C_6 acyl. Each R may independently be C_7 acyl. Each R may independently be C_8 acyl. Each R may independently be C_9 acyl. Each R may independently be C_{10} acyl.

Each of R^1, R^2, R^3 and R^4 may independently be linear or branched, substituted or unsubstituted, saturated or unsaturated C_1-C_{10} alkyl, or R^1 and R^2 or R^3 and R^4 may independently together form a substituted or unsubstituted, saturated or unsaturated cyclic C_3-C_{10} alkyl. Each of R^1, R^2, R^3 and R^4 may independently be branched or unbranched, substituted or unsubstituted, saturated or unsaturated C_1-C_{10} alkyl. Each of R^1, R^2, R^3 and R^4 may independently be branched or unbranched, substituted or unsubstituted, saturated or unsaturated C_1-C_9 alkyl. Each of R^1, R^2, R^3 and R^4 may independently be branched or unbranched, substituted or unsubstituted,

saturated or unsaturated C_1-C_8 alkyl. Each of R^1, R^2, R^3 and R^4 may independently be branched or unbranched, substituted or unsubstituted, saturated or unsaturated C_1-C_7 alkyl. Each of R^1, R^2, R^3 and R^4 may independently be branched or unbranched, substituted or unsubstituted, saturated or unsaturated C_1-C_6 alkyl. Each of R^1, R^2, R^3 and R^4 may independently be branched or unbranched, substituted or unsubstituted, saturated or unsaturated C_1-C_5 alkyl. Each of R^1, R^2, R^3 and R^4 may independently be branched or unbranched, substituted or unsubstituted, saturated or unsaturated C_1-C_4 alkyl. Each of R^1, R^2, R^3 and R^4 may independently be branched or unbranched, substituted or unsubstituted, saturated or unsaturated C_1-C_3 alkyl. Each of R^1, R^2, R^3 and R^4 may independently be branched or unbranched, substituted or unsubstituted, saturated or unsaturated C_1-C_2 alkyl. Each of R^1, R^2, R^3 and R^4 may be CH_3. R^1 and R^2 together may form a substituted or unsubstituted, saturated or unsaturated cyclic C_3-C_{10} alkyl. R^1 and R^2 together may form an unsubstituted, saturated cyclic C_6 alkyl. R^3 and R^4 together may form a substituted or unsubstituted, saturated or unsaturated cyclic C_3-C_{10} alkyl. R^3 and R^4 together may form an unsubstituted, saturated cyclic C_6 alkyl. Each of R^1 and R^2 and R^3 and R^4 may together form a substituted or unsubstituted, saturated or unsaturated cyclic C_3-C_{10} alkyl. Each of R^1 and R^2 and R^3 and R^4 may together form an unsubstituted, saturated cyclic C_6 alkyl.

Each R^5 may independently be unsubstituted C_1-C_{10} alkyl. Each R^5 may independently be unsubstituted C_1-C_9 alkyl. Each R^5 may independently be unsubstituted C_1-C_8 alkyl. Each R^5 may independently be unsubstituted C_1-C_7 alkyl. Each R^5 may independently be unsubstituted C_1-C_6 alkyl. Each R^5 may independently be unsubstituted C_1-C_5 alkyl. Each R^5 may independently be unsubstituted C_1-C_4 alkyl. Each R^5 may independently be unsubstituted C_1-C_3 alkyl. Each R^5 may independently be unsubstituted C_1-C_2 alkyl. Each R^5 may independently be unsubstituted C_1 alkyl. Each R^5 may independently be unsubstituted C_2 alkyl. Each R^5 may independently be unsubstituted C_3 alkyl. Each R^5 may independently be unsubstituted C_4 alkyl. Each R^5 may independently be unsubstituted C_5 alkyl. Each R^5 may independently be unsubstituted C_6 alkyl. Each R^5 may independently be unsubstituted C_7 alkyl. Each R^5 may independently be unsubstituted C_8 alkyl. Each R^5 may independently be unsubstituted C_9 alkyl. Each R^5 may independently be unsubstituted C_{10} alkyl.

Each R^6 may independently be C_1-C_{10} acyl. Each R^6 may independently be C_1-C_9 acyl. Each R^6 may independently be C_1-C_8 acyl. Each R^6 may independently

be C_1-C_7 acyl. Each R^6 may independently be C_1-C_6 acyl. Each R^6 may independently be C_1-C_5 acyl. Each R^6 may independently be C_1-C_4 acyl. Each R^6 may independently be C_1-C_3 acyl. Each R^6 may independently be C_1-C_2 acyl. Each R^6 may independently be C_1 acyl. Each R^6 may independently be C_2 acyl. Each R^6 may independently be C_3 acyl. Each R^6 may independently be C_4 acyl. Each R^6 may independently be C_5 acyl. Each R^6 may independently be C_6 acyl. Each R^6 may independently be C_7 acyl. Each R^6 may independently be C_8 acyl. Each R^6 may independently be C_9 acyl. Each R^6 may independently be C_{10} acyl.

R^7, R^8, R^9, R^{10}. R^{11} and R^{12} are each independently hydrogen, halo, or linear or branched, substituted or unsubstituted, saturated or unsaturated C_1-C_{10} alkyl. R^7, R^8, R^9, R^{10}. R^{11} and R^{12} are each independently hydrogen. At least one of R^7, R^8, R^9, R^{10}. R^{11} or R^{12} is independently hydrogen. R^7, R^8, R^9, R^{10}. R^{11} and R^{12} are each independently fluoro. At least one of R^7, R^8, R^9, R^{10}. R^{11} or R^{12} is independently fluoro. R^7, R^8, R^9, R^{10}. R^{11} and R^{12} are each independently chloro. At least one of R^7, R^8, R^9, R^{10}. R^{11} or R^{12} is independently chloro. R^7, R^8, R^9, R^{10}. R^{11} and R^{12} are each independently bromo. At least one of R^7, R^8, R^9, R^{10}. R^{11} or R^{12} is independently bromo. R^7, R^8, R^9, R^{10}. R^{11} and R^{12} are each independently methyl. At least one of R^7, R^8, R^9, R^{10}. R^{11} or R^{12} is independently methyl. R^7, R^8, R^9, R^{10}. R^{11} and R^{12} are each independently ethyl. At least one of R^7, R^8, R^9, R^{10}. R^{11} or R^{12} is independently ethyl. R^7, R^8, R^9, R^{10}. R^{11} and R^{12} are each independently C_3 alkyl. At least one of R^7, R^8, R^9, R^{10}. R^{11} or R^{12} is independently C_3 alkyl. R^7, R^8, R^9, R^{10}. R^{11} and R^{12} are each independently C_4 alkyl. At least one of R^7, R^8, R^9, R^{10}. R^{11} or R^{12} is independently C_4 alkyl. R^7, R^8, R^9, R^{10}. R^{11} and R^{12} are each independently C_5 alkyl. At least one of R^7, R^8, R^9, R^{10}. R^{11} or R^{12} is independently C_5 alkyl. R^7, R^8, R^9, R^{10}. R^{11} and R^{12} are each independently C_6 alkyl. At least one of R^7, R^8, R^9, R^{10}. R^{11} or R^{12} is independently C_6 alkyl. R^7, R^8, R^9, R^{10}. R^{11} and R^{12} are each independently C_7 alkyl. At least one of R^7, R^8, R^9, R^{10}. R^{11} or R^{12} is independently C_7 alkyl. R^7, R^8, R^9, R^{10}. R^{11} and R^{12} are each independently C_8 alkyl. At least one of R^7, R^8, R^9, R^{10}. R^{11} or R^{12} is independently C_8 alkyl. R^7, R^8, R^9, R^{10}. R^{11} and R^{12} are each independently C_9 alkyl. At least one of R^7, R^8, R^9, R^{10}. R^{11} or R^{12} is independently C_9 alkyl. R^7, R^8, R^9, R^{10}. R^{11} and R^{12} are each independently C_{10} alkyl. At least one of R^7, R^8, R^9, R^{10}. R^{11} or R^{12} is independently C_{10} alkyl.

The compounds described herein are meant to include all racemic mixtures and all individual enantiomers or combinations thereof, whether or not they are specifically depicted herein. Alternatively, one or more of the OH groups on the above compounds may be substituted to replace the H with a moiety selected from TABLE 1.

In yet other embodiments, the present disclosure provide the use of any of the compounds disclosed herein for modulating androgen receptor (AR) activity. For example, in certain embodiments modulating androgen receptor (AR) activity is in a mammalian cell.

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

The present disclosure also provides a method of modulating androgen receptor (AR) activity, the method comprising administering any of the compounds disclosed herein, or pharmaceutically acceptable salt thereof, to a subject in need thereof. For example, in certain specific embodiments modulating androgen receptor (AR) activity is for the treatment of one or more of the following: prostate cancer, breast cancer, ovarian cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, and age-related macular degeneration. In certain embodiments, the spinal and bulbar muscular atrophy is Kennedy's disease.

The present disclosure also provides a pharmaceutical composition comprising any one or more of the compounds disclosed herein and a pharmaceutically acceptable carrier. The pharmaceutical composition may be for treating one or more of the following: prostate cancer, breast cancer, ovarian cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary

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

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

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

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

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

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

TABLE 1. Amino Acid, Polyethylene Glycol, and Phosphate Based Moieties

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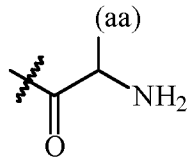
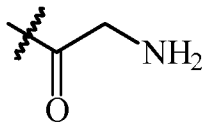
<tr><td> 

(aa) = any naturally occurring amino acid side chain</td><td> 
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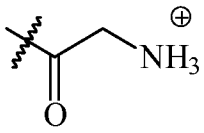
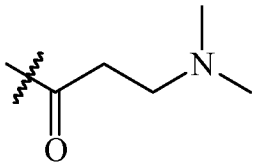
<tr><td> 
</td><td> 
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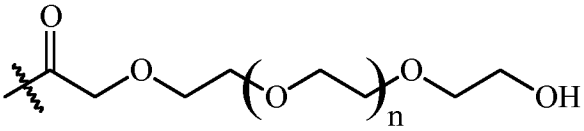
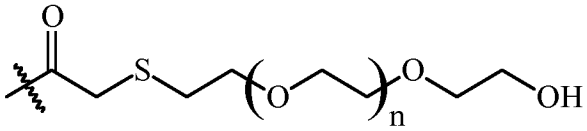
<tr><td> 

n = 1-200</td><td> 

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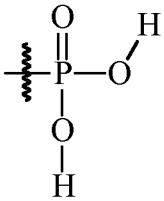
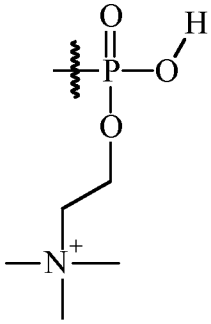
<tr><td> 
</td><td> 
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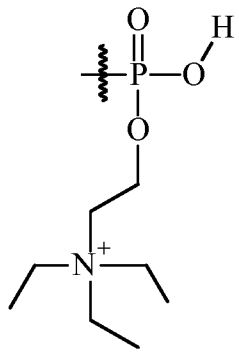
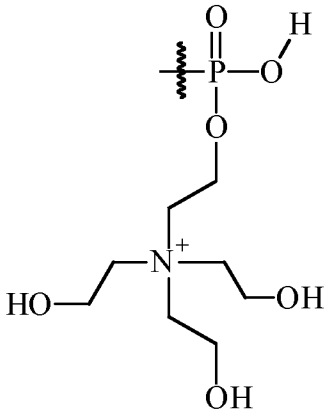
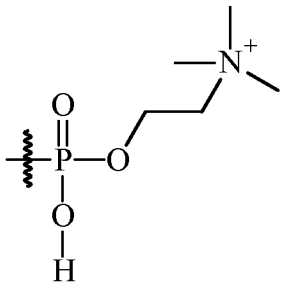
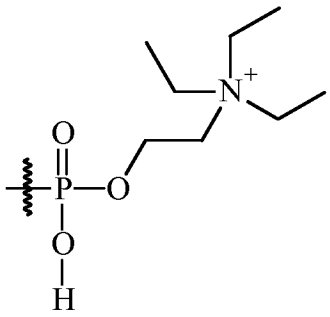
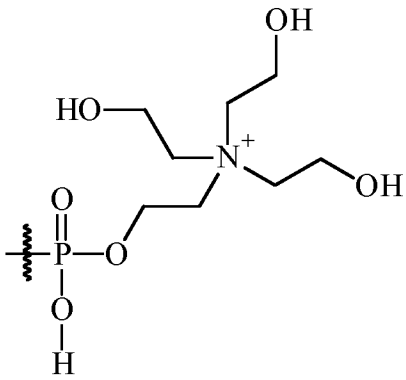
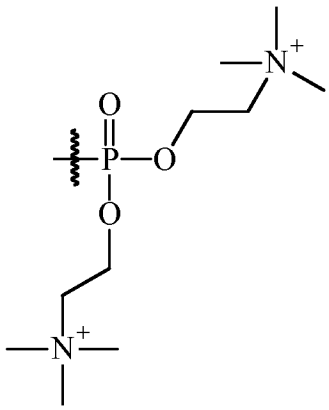
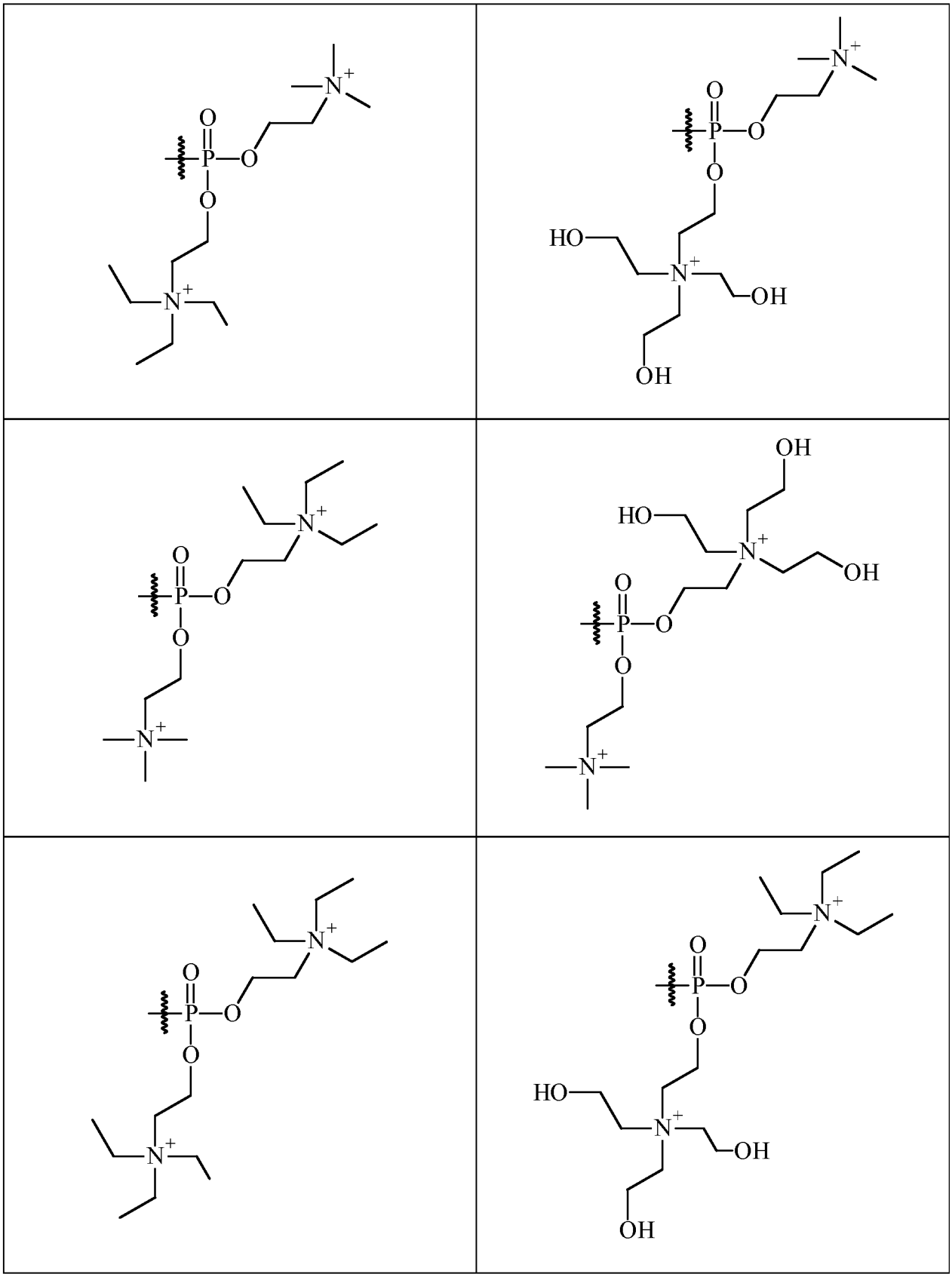
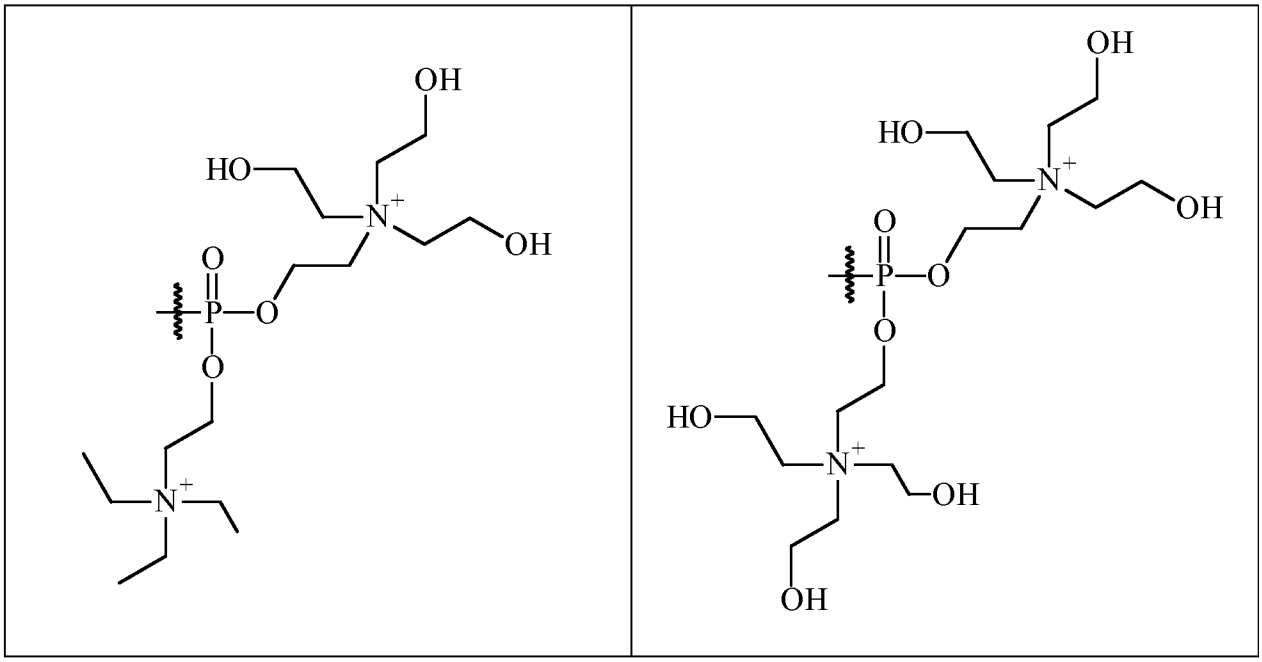
	
	
	





Moieties from TABLE 1 may be, for example, and without limitation, subdivided into three groups: 1) amino acid based moieties; 2) polyethylene glycol based moieties; and 3) phosphate based moieties. In the Moieties Table 1 above, the first four moieties are amino acid based moieties, the fifth and sixth are polyethylene glycol based moieties and the remaining moieties are phosphate based moieties.

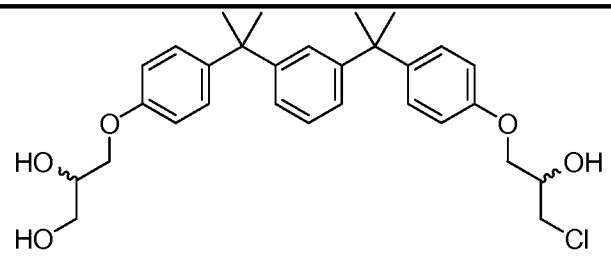
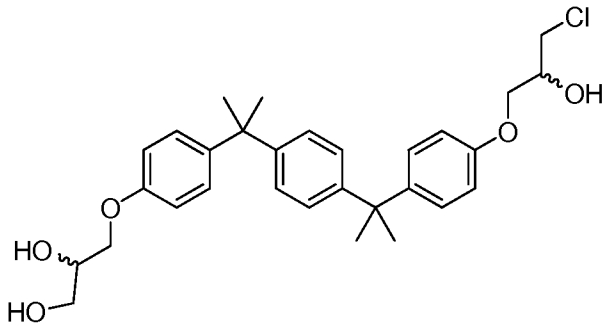
The amino acid side chains of naturally occurring amino acids (as often denoted herein using "(aa)") are well known to a person of skill in the art and may be found in a variety of text books such as "Molecular Cell Biology" by James Darnell *et al*. Third Edition, published by Scientific American Books in 1995. Often the naturally occurring amino acids are represented by the formula $(NH_2)C(COOH)(H)(R)$, where the chemical groups in brackets are each bonded to the carbon not in brackets. R represents the side chains in this particular formula.

Those skilled in the art will appreciate that the point of covalent attachment of the moiety to the compounds as described herein may be, for example, and without limitation, cleaved under specified conditions. Specified conditions may include, for example, and without limitation, *in vivo* enzymatic or non-enzymatic means. Cleavage of the moiety may occur, for example, and without limitation, spontaneously, or it may be catalyzed, induced by another agent, or a change in a physical parameter or environmental parameter, for example, an enzyme, light, acid, temperature or pH. The moiety may be, for example, and without limitation, a

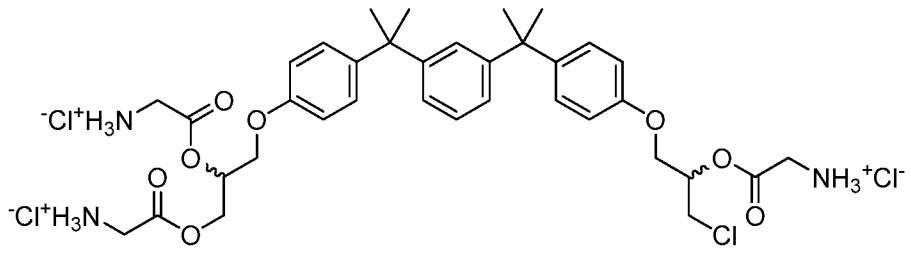
protecting group that acts to mask a functional group, a group that acts as a substrate for one or more active or passive transport mechanisms, or a group that acts to impart or enhance a property of the compound, for example, solubility, bioavailability or localization.

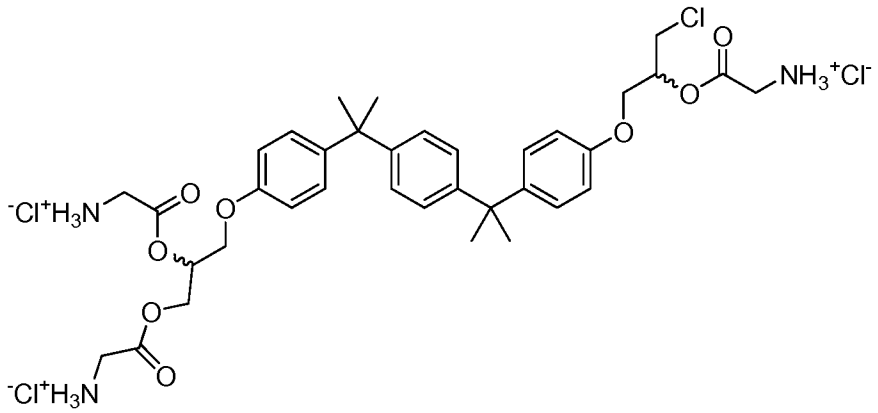
In other particular embodiments of the compounds as described anywhere herein, the following compounds in Table 2 are provided.

TABLE 2. Representative Compounds

No.	Structure	Name
6		3-(4-(2-(3-(2-(4-(3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenyl)propan-2-yl)phenoxy)propane-1,2-diol
10		3-(4-(2-(4-(2-(4-(3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenyl)propan-2-yl)phenoxy)propane-1,2-diol

Prodrugs are also included within the scope of the present disclosure. For example, in one embodiment the hydrogen atom of one or more hydroxyl groups of any of the compounds of Formula I may be replaced with a moiety from Table 1. Non-limiting examples of such prodrugs include glycine esters and salts thereof as shown below.





In some embodiments, the compounds as described herein or acceptable salts thereof above may be used for systemic 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. In some embodiments, the compounds as described herein or acceptable salts thereof above may be used in the preparation of a medicament or a composition for systemic treatment of an indication described herein. In some embodiments, methods of systemically treating any of the indications described herein are also provided. Some aspects of this invention, make use of compositions comprising a compound described herein and a pharmaceutically acceptable excipients or carrier. In some embodiments, the prostate cancer is castration-resistant prostate cancer (also referred to as hormone refractory, androgen-independent, androgen deprivation resistant, androgen ablation resistant, androgen depletion-independent, castration-recurrent, anti-androgen-recurrent). In some embodiments the prostate cancer is androgen-dependent or androgen-sensitive. Methods of 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.

Compounds as described herein may be in the free form or in the form of a salt thereof. In some embodiments, compounds as described herein may be in the form of a pharmaceutically acceptable salt, which are known in the art (Berge et al., *J. Pharm. Sci.* 1977, 66, 1). Pharmaceutically acceptable salt as used herein includes, for

example, salts that have the desired pharmacological activity of the parent compound (salts which retain the biological effectiveness and/or properties of the parent compound and which are not biologically and/or otherwise undesirable). Compounds as described herein having one or more functional groups capable of forming a salt may be, for example, formed as a pharmaceutically acceptable salt. Compounds containing one or more basic functional groups may be capable of forming a pharmaceutically acceptable salt with, for example, a pharmaceutically acceptable organic or inorganic acid. Pharmaceutically acceptable salts may be derived from, for example, and without limitation, acetic acid, adipic acid, alginic acid, aspartic acid, ascorbic acid, benzoic acid, benzenesulfonic acid, butyric acid, cinnamic acid, citric acid, camphoric acid, camphorsulfonic acid, cyclopentanepropionic acid, diethylacetic acid, digluconic acid, dodecylsulfonic acid, ethanesulfonic acid, formic acid, fumaric acid, glucoheptanoic acid, gluconic acid, glycerophosphoric acid, glycolic acid, hemisulfonic acid, heptanoic acid, hexanoic acid, hydrochloric acid, hydrobromic acid, hydriodic acid, 2-hydroxyethanesulfonic acid, isonicotinic acid, lactic acid, malic acid, maleic acid, malonic acid, mandelic acid, methanesulfonic acid, 2-napthalenesulfonic acid, naphthalenedisulphonic acid, p-toluenesulfonic acid, nicotinic acid, nitric acid, oxalic acid, pamoic acid, pectinic acid, 3-phenylpropionic acid, phosphoric acid, picric acid, pimelic acid, pivalic acid, propionic acid, pyruvic acid, salicylic acid, succinic acid, sulfuric acid, sulfamic acid, tartaric acid, thiocyanic acid or undecanoic acid. Compounds containing one or more acidic functional groups may be capable of forming pharmaceutically acceptable salts with a pharmaceutically acceptable base, for example, and without limitation, inorganic bases based on alkaline metals or alkaline earth metals or organic bases such as primary amine compounds, secondary amine compounds, tertiary amine compounds, quaternary amine compounds, substituted amines, naturally occurring substituted amines, cyclic amines or basic ion-exchange resins. Pharmaceutically acceptable salts may be derived from, for example, and without limitation, a hydroxide, carbonate, or bicarbonate of a pharmaceutically acceptable metal cation such as ammonium, sodium, potassium, lithium, calcium, magnesium, iron, zinc, copper, manganese or aluminum, ammonia, benzathine, meglumine, methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, triethylamine, isopropylamine, tripropylamine, tributylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine,

histidine, caffeine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, glucamine, methylglucamine, theobromine, purines, piperazine, piperidine, procaine, N-ethylpiperidine, theobromine, tetramethylammonium compounds, tetraethylammonium compounds, pyridine, N,N-dimethylaniline, N-methylpiperidine, morpholine, N-methylmorpholine, N-ethylmorpholine, dicyclohexylamine, dibenzylamine, N,N-dibenzylphenethylamine, 1-ephenamine, N,N'-dibenzylethylenediamine or polyamine resins. In some embodiments, compounds as described herein may contain both acidic and basic groups and may be in the form of inner salts or zwitterions, for example, and without limitation, betaines. Salts as described herein may be prepared by conventional processes known to a person skilled in the art, for example, and without limitation, by reacting the free form with an organic acid or inorganic acid or base, or by anion exchange or cation exchange from other salts. Those skilled in the art will appreciate that preparation of salts may occur *in situ* during isolation and purification of the compounds or preparation of salts may occur by separately reacting an isolated and purified compound.

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

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

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.

In some embodiments, pharmaceutical compositions in accordance with this invention may 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 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.

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

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

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

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

It is to be noted that dosage values may vary with the severity of the condition to be alleviated. For any particular subject, specific dosage regimens may be adjusted over time according to the individual need and the professional judgement of the person administering or supervising the administration of the compositions. Dosage ranges set forth herein are exemplary only and do not limit the dosage ranges that may be selected by medical practitioners. The amount of active compound(s) in the composition may vary according to factors such as the disease state, age, sex, and

weight of the subject. Dosage regimens may be adjusted to provide the optimum therapeutic response. For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It may be advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage.

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

With respect to combination therapies, one embodiment of the present disclosure provides a combination of any one or more of a compound of Formula I with one or more currently-used or experimental pharmacological therapies which are or may be utilized to treat any of the above disease states (e.g., androgen-independent prostate cancer or Kennedy's disease). Methods, uses and pharmaceutical compositions comprising the above combination are also provided. Combination therapies for such indications are disclosed in co-pending U.S. Provisional Application No. 61/384,628, which is hereby incorporated by reference in its entirety.

Surprisingly, it has been found that the disclosed compounds, which interfere with the AR principally through binding to the N-terminus of the AR, demonstrate beneficial synergistic therapeutic effects when used in concert with existing approved and in-development agents. That is, the biological impact of using the agents in concert with one another produces a biological and therapeutic effect which is greater than the simple additive effect of each of them separately.

Accordingly, one embodiment comprises the use of the disclosed compounds in combination therapy with one or more currently-used or experimental

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

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

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

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

For greater clarity the compound(s) of Formula I that are combined with the one or more Other Therapeutic Agents for improved treatment of the above disease

states may comprise, but are not limited to any compound having a structure of Formula I, including those compounds shown in Table 2.

The Other Therapeutic Agents include without limitation any pharmacological agent which is currently approved by the FDA in the U.S. (or elsewhere by any other regulatory body) for use as pharmacological treatment of any of the above disease states, or which is currently being used experimentally as part of a clinical trial program that relates to the above disease states. Non-limiting examples of the Other Pharmacological Agents comprise, without limitation: the chemical entity known as MDV3100 (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 AR LBD and is currently in development as a treatment for prostate cancer; the chemical entity known as TOK 001 and related compounds which appears to be a blocker of the AR LBD, and a CYP17 lyase inhibitor, and also appears to decrease overall androgen receptor levels in prostate cancer cells. TOK 001 is currently in development as a treatment for prostate cancer; the chemical entity known as ARN-509 and related compounds which appears to be a blocker of the 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 is currently in development for the treatment of prostate cancer; the chemical entity known as bicalutamide (N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methylpropanamide) and related compounds, which appears to be a blocker of the 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 AR LBD and which is currently used to treat prostate cancer, the chemical entities know as cyproterone acetate (6-chloro-1β,2β-dihydro-17-hydroxy-3′H-cyclopropa[1,2]pregna-4,6-diene-3,20-dione) and related compounds, which appears to be a blocker of the AR LBD and which is currently used

to treat prostate cancer, the chemical entity known as docetaxel (Taxotere; 1,7β,10β-trihydroxy-9-oxo-5β,20-epoxytax-11-ene-2α,4,13α-triyl 4-acetate 2-benzoate 13-{(2R,3S)-3-[(tert-butoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoate}) and related compounds, which appears to be a cytotoxic antimicrotubule agent and is currently used in combination with prednisone to treat prostate cancer, the chemical entity known as Bevacizumab (Avastin), a monoclonal antibody that recognizes and blocks vascular endothelial growth factor A (VEGF-A) and may be used to treat prostate cancer, the chemical entity known as OSU-HDAC42 ((S)-(+)-N-hydroxy-4-(3-methyl-2-phenylbutyrylamino)-benzamide), and related compounds, which appears to act as a histone deacetylase inhibitor, and is currently being developed as a treatment for prostate cancer, the chemical entity known as VITAXIN which appears to be a monoclonal antibody against the vascular integrin αvβ3 to prevent angiogenesis, and which may be used to treat prostate cancer, the chemical entity known as sunitumib (N-(2-diethylaminoethyl)-5-[(Z)-(5-fluoro-2-oxo-1H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide) and related compounds, which appears to inhibit multiple receptor tyrosine kinases (RTKs) and may be used for treatment of prostate cancer, the chemical entity known as ZD-4054 (N-(3-Methoxy-5-methylpyrazin-2-yl)-2-[4-(1,3,4-oxadiazol-2-yl)phenyl]pyridin-3-sulfonamid) and related compounds, which appears to block the edta receptor and which may be used for treatment of prostate cancer, the chemical entity known as VN/124-1 (3β-Hydroxy-17-(1H-benzimidazol-1-yl)androsta-5,16-diene), and related compounds which appears to block the production of androgen (via inhibition of -hydroxylase/17,20 lyase) and is currently in development for the treatment of prostate cancer; the chemical entity known as Cabazitaxel (XRP-6258), and related compounds, which appears to be a cytotoxic microtubule inhibitor, and which is currently used to treat prostate cancer; the chemical entity known as MDX-010 (Ipilimumab), a fully human monoclonal antibody that binds to and blocks the activity of CTLA-4 which is currently in development as an immunotherapeutic agent for treatment of prostate cancer; the chemical entity known as OGX 427 which appears to target HSP27 as an antisense agent, and which is currently in development for treatment of prostate cancer; the chemical entity known as OGX 011 which appears to target clusterin as an antisense agent, 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-(5α,17β)-4-azaandrost-1-ene-17-

carboxamide), and related compounds, which appears to be a 5-alpha reductase inhibitor that reduces levels of dihydrotestosterone, and may be used to treat prostate cancer; the chemical entity known as dutasteride (Avodart; 5α, 17β)-N-{2,5 bis(trifluoromethyl) phenyl}-3-oxo-4-azaandrost-1-ene-17-carboxamide) and related molecules, which appears to be a 5-alpha reductase inhibitor that reduces levels of dihydrotestosterone, and may be used in the treatment of prostate cancer; the chemical entity known as turosteride ((4aR,4bS,6aS,7S,9aS,9bS,11aR)-1,4a,6a-trimethyl-2-oxo-N-(propan-2-yl)-N-(propan-2 ylcarbamoyl)hexadecahydro-1H-indeno[5,4-f]quinoline-7-carboxamide), and related molecules, which appears to be a 5-alpha reductase inhibitor that reduces levels of dihydrotestosterone and may be used in the treatment of prostate cancer; the chemical entity known as bexlosteride (LY-191,704; (4aS,10bR)-8-chloro-4-methyl-1,2,4a,5,6,10b-hexahydrobenzo[f]quinolin-3-one), and related compounds, which appears to be a 5-alpha reductase inhibitor that reduces levels of dihydrotestosterone and may be used in the treatment of prostate cancer; the chemical entity known as izonsteride (LY-320,236; (4aR,10bR)-8-[(4-ethyl-1,3-benzothiazol-2-yl)sulfanyl]-4,10b-dimethyl-1,4,4a,5,6,10b-hexahydrobenzo[f]quinolin-3(2H)-one) and related compounds, which appears to be a 5-alpha reductase inhibitor that reduces levels of dihydrotestosterone and may be used for the treatment of prostate cancer; the chemical entity known as FCE 28260 and related compounds, which appears to be a 5-alpha reductase inhibitor that reduces levels of dihydrotestosterone and may be used for the treatment of prostate cancer; the chemical entity known as SKF105,111, and related compounds, which appears to be a 5-alpha reductase inhibitor that reduces levels of dihydrotestosterone and may be used for treatment of prostate cancer.

In general, compounds of the invention should be used without causing substantial 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 however, such as in severe disease conditions, it may be necessary to administer substantial excesses of the compositions. Some compounds of this invention may be toxic at some concentrations. Titration studies may be used to determine toxic and non-toxic concentrations. Toxicity may be evaluated by examining a particular compound's or composition's specificity across cell lines using

PC3 cells as a negative control that do not express functional AR. Animal studies may be used to provide an indication if the compound has any effects on other tissues. Systemic therapy that targets the AR will not likely cause major problems to other tissues since antiandrogens and androgen insensitivity syndrome are not fatal.

Compounds as described herein may be administered to a subject. As used herein, a "subject" may be a human, non-human primate, mammal, rat, mouse, cow, horse, pig, sheep, goat, dog, cat and the like. The subject may be suspected of having or at risk for having a cancer, such as prostate cancer, breast cancer, ovarian cancer, salivary gland carcinoma, or endometrial cancer, or suspected of having or at risk for having acne, hirsutism, alopecia, benign prostatic hyperplasia, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, or age-related macular degeneration. Diagnostic methods for various cancers, such as prostate cancer, breast cancer, ovarian cancer, salivary gland carcinoma, or endometrial cancer, and diagnostic methods for acne, hirsutism, alopecia, benign prostatic hyperplasia, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, or age-related macular degeneration and the clinical delineation of cancer, such as prostate cancer, breast cancer, ovarian cancer, salivary gland carcinoma, or endometrial cancer, diagnoses and the clinical delineation of acne, hirsutism, alopecia, benign prostatic hyperplasia, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, or age-related macular degeneration are known to those of ordinary skill in the art.

Compounds described herein may be used 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. Compounds described herein may be used for treatment of prostate cancer. Compounds described herein may be used for treatment of castration-resistant prostate cancer. Compounds described herein may be used for treatment of androgen-dependent prostate cancer. Compounds described herein may be used for preparation of a medicament 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. Compounds described herein may be used for the preparation of a medicament for treatment of prostate cancer. Compounds described herein may be used for the preparation of a medicament for treatment of castration-resistant prostate cancer. Compounds described herein may be used for the preparation of a medicament for treatment of androgen-dependent prostate cancer. Compounds described herein may be used in a method 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. The method may comprise administering to a subject in need thereof an effective amount of a compound described herein. Compounds described herein may be used in a method of treatment of prostate cancer, the method comprising administering to a subject in need thereof an effective amount of a compound described herein. Compounds described herein may be used in a method of treatment of castration resistant prostate cancer, the method comprising administering to a subject in need thereof an effective amount of a compound described herein. Compounds described herein may be used in a method of treatment of androgen-dependent prostate cancer, the method comprising administering to a subject in need thereof an effective amount of a compound described herein.

Compounds described herein may also be used in assays and for research purposes. Definitions used include ligand-dependent activation of the androgen receptor (AR) by androgens such as dihydrotestosterone (DHT) or the synthetic androgen (R1881) used for research purposes. Ligand-independent activation of the AR refers to transactivation of the AR in the absence of androgen (ligand) by, for example, stimulation of the cAMP-dependent protein kinase (PKA) pathway with forskolin (FSK). Some compounds and compositions of this invention may inhibit both FSK and androgen (e.g. R1881) induction of ARE-luciferase (ARE-luc). Constituative activity of the AR refers to splice variants lacking the AR ligand-binding domain. Such compounds may block a mechanism that is common to both ligand-dependent and ligand-independent activation of the AR, as well as constitutively active splice variants of the AR that lack ligand-binding domain. This could involve any step in activation of the AR including dissociation of heatshock proteins, essential posttranslational modifications (e.g., acetylation, phosphorylation), nuclear translocation, protein-protein

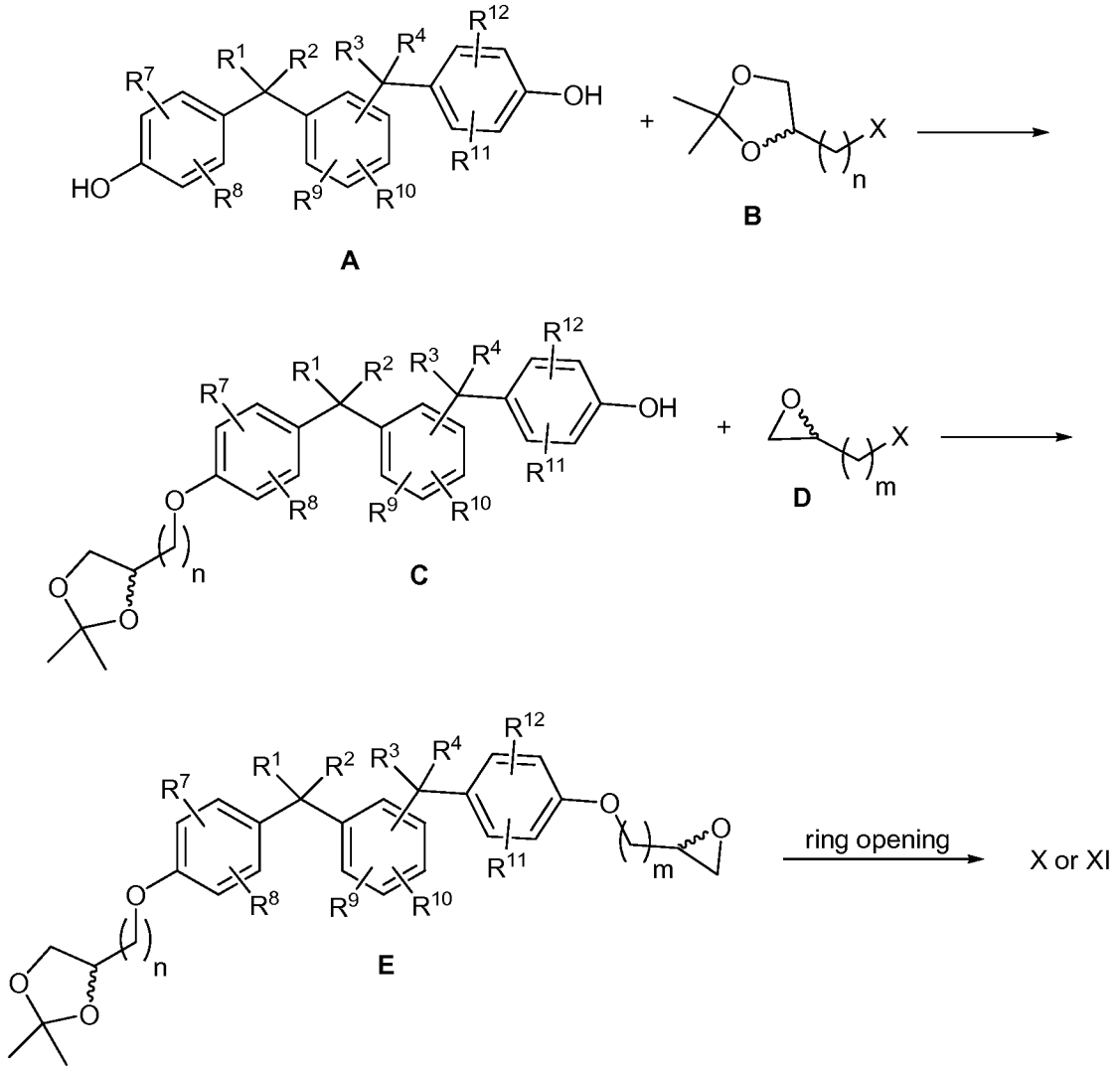
interactions, formation of the transcriptional complex, release of co-repressors, and/or increased degradation. Some compounds and compositions of this invention may inhibit ligand-only activityand may interfere with a mechanism specific to ligand-dependent activation (e.g., accessibility of the ligand binding domain (LBD) to androgen). Numerous disorders in addition to prostate cancer involve the androgen axis (e.g., acne, hirsutism, alopecia, benign prostatic hyperplasia) and compounds interfering with this mechanism may be used to treat such conditions. Some compounds and compositions of this invention may only inhibit FSK induction and may be specific inhibitors to ligand-independent activation of the AR. These compounds and compositions may interfere with the cascade of events that normally occur with FSK and/or PKA activity or any downstream effects that may play a role on the AR (e.g. FSK increases MAPK activity which has a potent effect on AR activity). Examples may include an inhibitor of cAMP and or PKA or other kinases. Some compounds and compositions of this invention may induce basal levels of activity of the AR (no androgen or stimulation of the PKA pathway). Some compounds and compositions of this invention may increase induction by R1881 or FSK. Such compounds and compositions may stimulate transcription or transactivation of the AR. Some compounds and compositions of this invention may inhibit activity of the androgen receptor. Interleukin-6 (IL-6) also causes ligand-independent activation of the AR in LNCaP cells and can be used in addition to FSK.

Compounds for use in the present invention may be obtained from medical sources or modified using known methodologies from naturally occurring compounds. In addition, methods of preparing or synthesizing compounds of the present 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 suitable synthetic procedures that may be considered and suitably adapted for preparing compounds of any one of the Formula I to XXI as set out above. Other references that may be helpful include: Debasish Das, Jyh-Fu Lee and Soofin Cheng "Sulfonic acid functionalized mesoporous MCM-41 silica as a convenient catalyst for Bisphenol-A synthesis" *Chemical Communications*, (2001) 2178–2179; US Patent 2571217 Davis, Orris L.; Knight, Horace S.; Skinner, John R. (Shell Development Co.) "Halohydrin ethers of phenols." (1951); and Rokicki, G.; Pawlicki, J.; Kuran, W. "Reactions of

4-chloromethyl-1,3-dioxolan-2-one with phenols as a new route to polyols and cyclic carbonates." Journal fuer Praktische Chemie (Leipzig) (1985) 327, 718-722.

For example, compounds of the present invention which contain an ether moiety (*e.g.,* compounds having Formulas X or XI) may be obtained with reference to the following general chemical synthetic Scheme I:

General Reaction Scheme



Referring to the above General Reaction Scheme, compounds of structure **A**, wherein R^1-R^{12} are as defined herein, can be purchased or prepared according to methods known in the art. Reaction of **A** with acetonide **B**, wherein n is as defined herein and X is a suitable leaving group (*e.g.*, chloro and the like), produces compounds of structure **C**. Subsequent reaction of **C** with **D**, wherein m is as defined

herein and X is a suitable leaving group (*e.g.*, chloro and the like), yields **E**. Finally, opening of the acetonide and/or epoxide rings of **E** by treatment with a sutiable reagent (*e.g.*, $CeCl_3$, and the like) produces compounds of structure X or XII.

One skilled in the art will recognize that certain variations to the above general methodology are possible in order to prepare various embodiments of the present disclosure. For example, in one embodiment, a starting material comprising various Z^1, Z^2 and/or Z^3 moieties may be used to produce different compounds of structure I. In addition, the order of reaction may be changed and/or bis acetonides or bis epoxides may prepared and opened according to the above methodolgy. Further, various embodiments may be prepared without the use of the epoxide and/or acetonide intermediates shown above. For example, certain embodiments may be prepared by reaction of A with a suitable alkylating reagent to produce any of the ether-containing compounds described herein.

Various alternative embodiments and examples of the invention are described herein. These embodiments and examples are illustrative and should not be construed as limiting the scope of the invention.

EXAMPLES

All non-aqueous reactions were performed in flame-dried round bottomed flasks. The 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 aluminium plates pre-coated with 0.25 mm 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin-layer chromatography plates were visualized by exposure to ultraviolet light and a "Seebach" staining solution (700 mL water, 10.5 g Cerium (IV) sulphate tetrahydrate, 15.0 g molybdato phosphoric acid, 17.5 g sulphuric acid) followed by heating (~1 min) with a heating gun (~250 °C). Organic solutions were concentrated on Büchi R-114 rotatory evaporators at reduced pressure (15-30 torr, house vacuum) at 25-40 °C.

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

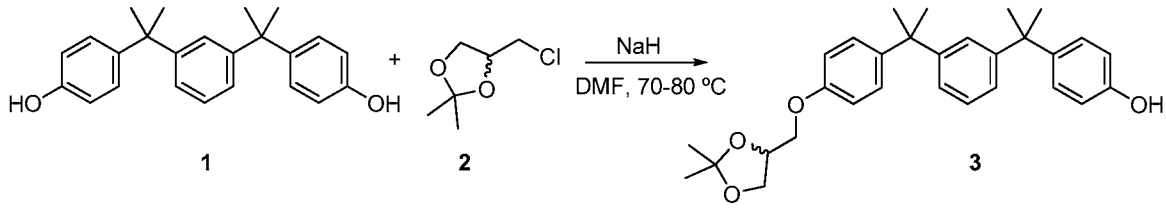
Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 25 °C using a Bruker 400 with inverse probe and Bruker 400 spectrometers, are reported in parts per million on the δ scale, and are referenced from the residual protium in the NMR solvent (DMSO-d_6: δ 2.50 (DMSO-d_5), $CDCl_3$: δ 7.24 ($CHCl_3$)). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Bruker 400 spectrometer, are reported in parts per million on the δ scale, and are referenced from the carbon resonances of the solvent (DMSO-d_6: δ 39.51, $CDCl_3$: δ 77.00). Spectral features are tabulated in the following order: chemical shift (δ, ppm); multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad); coupling constant (*J*, Hz, number of protons).

LNCaP cells were employed initially for all experiments because they are well-differentiated human prostate cancer cells in which ligand-independent activation of the AR by FSK has been characterized (Nazareth *et al* 1996 *J. Biol. Chem.*

271, 19900-19907; and Sadar 1999 *J. Biol. Chem.* 274, 7777-7783). LNCaP cells express endogenous AR and secrete prostate-specific antigen (PSA) (Horoszewicz *et al* 1983 *Cancer Res.* 43, 1809-1818). LNCaP cells can be grown either as monolayers in cell culture or as tumors in the well-characterized xenograft model that progresses to androgen independence in castrated hosts (Sato *et al* 1996 *J. Steroid Biochem. Mol. Biol.* 58, 139-146; Gleave *et al* 1991 *Cancer Res.* 51, 3753-3761; Sato *et al* 1997 *Cancer Res.* 57, 1584-1589; and Sadar *et al* 2002 *Mol. Cancer Ther.* 1(8), 629-637). R1881 was employed since it is stable and avoids problems associated with the labile physiological ligand dihydrotestosterone (DHT). Reporter specificity may be determined using several alternative reporter gene constructs. Some well characterized ARE-driven reporter gene constructs that have been used extensively are the PSA (6.1 kb) enhance/promoter which contains several AREs and is highly inducible by androgens as well as by FSK (Ueda *et al* 2002 A *J. Biol. Chem.* 277, 7076-7085) and the ARR3-thymidine kinase (tk)-luciferase, which is an artificial reporter construct that contains three tandem repeats of the rat probasin ARE1 and ARE2 regions upstream of a luciferase reporter (Snoek *et al* 1996 *J. Steroid Biochem. Mol. Biol.* 59, 243-250).

EXAMPLE 1

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

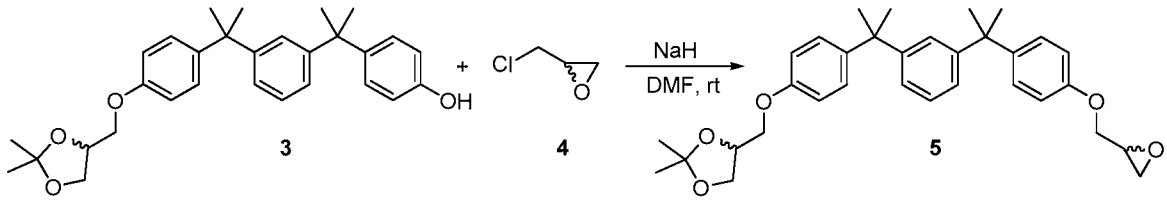


1 2 3

Sodium hydride (60% dispersion in mineral oil, 69 mg, 1.73 mmol, 1.2 equiv) was added slowly to a stirred solution of 4,4'-(1,3-Phenylenediisopropylidene)bisphenol **1** (500 mg, 1.44 mmol, 1 equiv) in anhydrous dimethyl formamide (8 mL), at room temperature, and the contents were stirred under an atmosphere of argon for 20 min. Racemic 4-chloromethyl-2,2-dimethyl-1,3-dioxolane **2** (245 μL, 1.73 mmol, 1.2 equiv) was added via syringe, and the mixture was allowed to react at 70-80 ° C for 40 h. Next, the reaction was quenched by the addition of a saturated solution of ammonium chloride (4 mL), and the mixture was extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with deionized water (10 mL), dried over anhydrous magnesium sulfate, filtered,and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 100% dichloromethane) to provide **3** (140 mg, 21%) as a yellow foam. Note: The same reaction also yielded the bis ketal analogue of 3. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-7.19 (m, 1H), 7.12 (d, J = 7.6, 2H), 7.08 (d, J = 8.8, 2H), 6.99 (d, J = 8.4, 2H), 6.85 (s, 1H), 6.78 (d, J = 8.8, 2H), 6.68 (d, J = 8.4, 2H), 6.10 (br, 1H), 4.57-4.53 (m, 1H), 4.24-4.20 (m, 1H), 4.10-4.07 (m, 1H), 4.03-3.96 (m, 2H), 1.64-1.61 (m, 12H), 1.55 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 153.8, 150.7, 150.6, 143.6, 142.7, 128.0, 127.9, 127.5, 126.9, 123.6, 123.4, 114.8, 113.9, 110.2 74.4, 68.7, 66.8, 42.5, 31.1, 31.0, 30.9, 30.9, 26.9, 25.6; HRMS (EI) (*m/z*): calc'd for $C_{30}H_{36}O_4$: 460.26136, found: 460.26093.

EXAMPLE 2

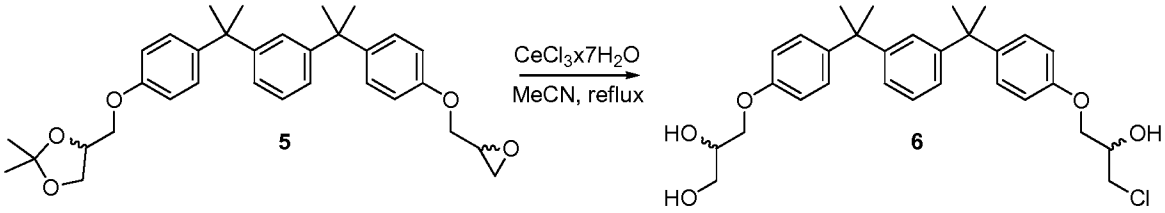
SYNTHESIS OF 2,2-DIMETHYL-4-((4-(2-(3-(2-(4-(OXIRAN-2-YLMETHOXY)PHENYL)PROPAN-2-YL)PHENYL)PROPAN-2-YL)PHENOXY)METHYL)-1,3-DIOXOLANE (**5**)



Sodium hydride (60% dispersion in mineral oil, 18 mg, 0.45 mmol, 1.5 equiv) was added slowly to a stirred solution of **3** (137 mg, 0.30 mmol, 1 equiv) in anhydrous dimethyl formamide (1 mL) at room temperature, and the contents were stirred under an atmosphere of argon for 20 min. Racemic epichlorohydrin **4** (47 μL, 0.59 mmol, 2.0 equiv) was added via syringe, and the mixture was allowed to react at room temperature for 22 h. Next, 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 (3 x 5 mL). The organic layer was washed with deionized water (5 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 40% ethyl acetate in hexane to 100% ethyl acetate) to provide **5** (127 mg, 83%) as a clear foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20-7.16 (m, 2H), 7.15-7.12 (dd, *J* = 8.8, 1.6, 4H), 7.06-7.04 (dd, *J* = 8.0, 1.6, 2H), 6.85-6.82 (dd, *J* = 8.4, 1.6, 4H), 4.52-4.49 (m, 1H), 4.23-4.15 (m, 2H), 4.10-4.06 (m, 1H), 3.99-3.91 (m, 3H), 3.38-3.35 (m, 1H), 2.91 (t, *J* = 4.8, 1H), 2.78-2.76 (dd, *J* = 4.8, 2.8, 1H), 1.65 (s, 12H), 1.55 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.5, 156.5, 150.4, 143.8, 143.7, 128.0, 127.9, 127.6, 125.5, 124.2, 114.1, 114.0, 109.8, 74.3, 69.0, 68.9, 67.1, 50.4, 44.9, 42.6, 31.1, 27.0, 25.6; HRMS (ESI) (*m/z*): calc'd for $C_{33}H_{40}O_5Na$ $[M+Na]^+$: 539.2773, found: 539.2776.

EXAMPLE 3

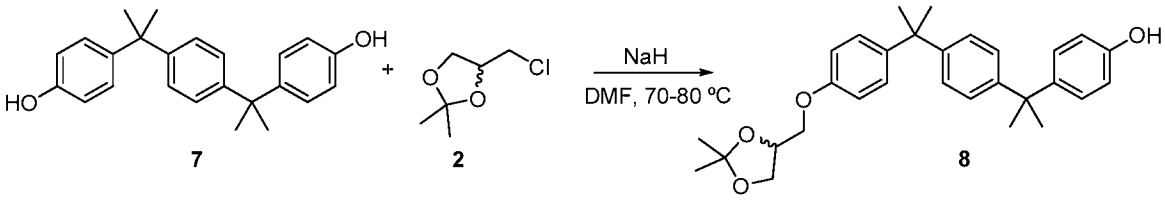
SYNTHESIS OF 3-(4-(2-(3-(2-(4-(3-CHLORO-2-HYDROXYPROPOXY)PHENYL)PROPAN-2-YL)PHENYL)PROPAN-2-YL)PHENOXY)PROPANE-1,2-DIOL (**6**)



To a solution of *racemic* **5** (127 mg, 0.24 mmol, 1 equiv) in acetonitrile (2 mL) was added $CeCl_3 \cdot 7H_2O$ (227 mg, 0.61 mmol, 2.5 equiv), and the mixture was refluxed for 22 h. The resulting white paste was filtered and washed with ethyl acetate, and the clear suspension was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 5% methanol in dichloromethane to 10% methanol) to provide **6** (65 mg, 52%) as a white foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.22 (m, 1H), 7.14-7.09 (m, 6H), 6.98 (m, 1H), 6.82-6.79 (dd, J = 8.8, 2.0, 4H), 4.28-4.23 (m, 1H), 4.18-4.13 (m, 1H), 4.11-4.10 (m, 2H), 4.06 (d, J = 5.2, 2H), 3.90-3.87 (dd, J = 11.6, 3.6, 1H), 3.84-3.74 (m, 3H), 1.65 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3, 156.1, 150.5, 150.4, 144.0, 143.9, 128.0, 128.0, 127.6, 126.6, 123.8, 114.0, 114.0, 70.7, 70.1, 69.4, 68.9, 68.8, 63.9, 46.1, 42.6, 31.1; HRMS (ESI) (*m/z*): calc'd for $C_{30}H_{37}O_5NaCl$ $[M+Na]^+$: 535.2227, found: 535.2235.

EXAMPLE 4

SYNTHESIS OF 4-(2-(4-(2-(4-((2,2-DIMETHYL-1,3-DIOXOLAN-4-YL)METHOXY)PHENYL)PROPAN-2-YL)PHENYL)PROPAN-2-YL)PHENOL (**8**)

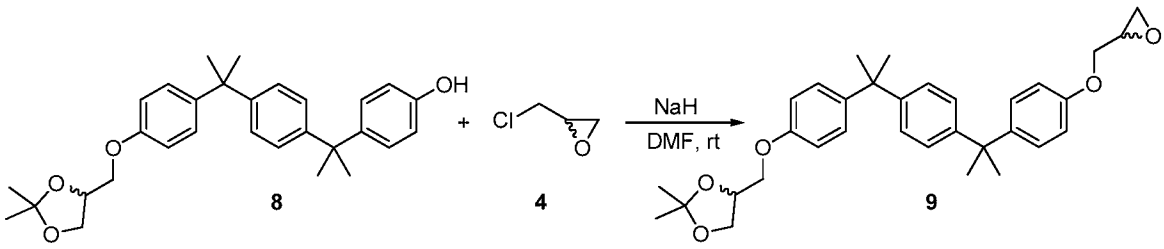


Sodium hydride (60% dispersion in mineral oil, 173 mg, 4.33 mmol, 1.5 equiv) was added slowly to a stirred solution of 4,4'-(1,4-

Phenylenediisopropylidene)bisphenol **7** (1000 mg, 2.88 mmol, 1 equiv) in anhydrous dimethyl formamide (10 mL) at room temperature, and the contents were stirred under an atmosphere of argon for 20 min. Racemic 4-chloromethyl-2,2-dimethyl-1,3-dioxolane **2** (613 μL, 4.33 mmol, 1.5 equiv) was added via syringe, and the mixture was allowed to react at 70-80 °C for 21 h. Then, the reaction was quenched by the addition of a saturated solution of ammonium chloride (5 mL), and the mixture was extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with deionized water (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 100% dichloromethane) to provide **8** (271 mg, 20%) as a colourless foam. Note: The same reaction yielded the bis ketal analogue of **8** as well. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-7.19 (m, 2H), 7.15-7.12 (m, 6H), 6.87- 6.84 (m, 2H), 6.77-6.75 (m, 2H), 5.78 (s, 1H), 4.55-4.52 (m, 1H), 4.24-4.20 (dd, J = 8.8, 6.8, 1H), 4.11-4.08 (dd, J = 9.6, 5.6, 1H), 3.99-3.94 (m, 2H), 1.68 (d, J = 4.0, 12H), 1.53 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.5, 153.7, 148.1, 148.0, 143.7, 143.0, 128.1, 128.0, 126.4, 126.4, 114.9, 114.1, 110.1, 74.3, 68.9, 67.1, 42.1, 42.0, 31.1, 31.1, 27.0, 25.6; HRMS (ESI) (*m/z*): calc'd for $C_{30}H_{36}O_4Na$ $[M+Na]^+$: 483.2511, found: 483.2503.

EXAMPLE 5

SYNTHESIS OF 2,2-DIMETHYL-4-((4-(2-(4-(2-(4-(OXIRAN-2-YLMETHOXY)PHENYL)PROPAN-2-YL)PHENYL)PROPAN-2-YL)PHENOXY)METHYL)-1,3-DIOXOLANE (9)

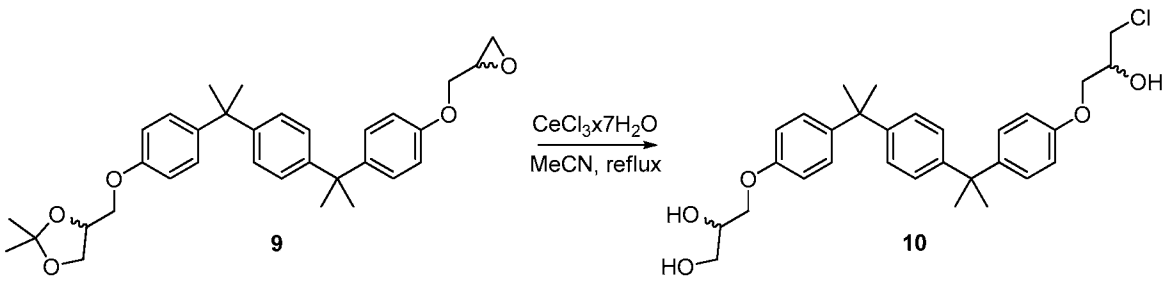


Sodium hydride (60% dispersion in mineral oil, 25 mg, 0.62 mmol, 1.5 equiv) was added slowly to a stirred solution of derivative **8** (191 mg, 0.41 mmol, 1 equiv) in anhydrous dimethyl formamide (1 mL) at room temperature, and the contents were stirred under an atmosphere of argon for 20 min. Racemic epichlorohydrin **4** (64

μL, 0.82 mmol, 2.0 equiv) was added via syringe, and the mixture was allowed to react at room temperature for 22 h. Then, 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 (3 x 5 mL). The organic layer was washed with deionized water (5 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 40% ethyl acetate in hexane to 50% ethyl acetate) to provide **9** (203 mg, 95%) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24-7.22 (m, 4H), 7.18 (br, 4H), 6.91-6.88 (m, 4H), 4.55-4.52 (m, 1H), 4.25-4.20 (m, 2H), 4.13-4.09 (dd, *J* = 9.6, 5.2, 1H), 4.02-3.94 (m, 3H), 3.39-3.38 (m, 1H), 2.94-2.92 (dd, *J* = 4.8, 4.4, 1H), 2.80-2.78 (dd, *J* = 4.8, 2.8, 1H), 1.68 (s, 12H), 1.53 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.6, 156.6, 148.1, 148.0, 143.7, 143.6, 128.0, 128.0, 126.4, 114.2, 114.1, 109.9, 74.3, 69.0, 69.0, 67.2, 50.4, 44.9, 42.1, 31.1, 27.1, 25.6; HRMS (ESI) (*m/z*): calc'd for $C_{33}H_{40}O_5Na$ $[M+Na]^+$: 539.2773, found: 539.2784.

EXAMPLE 6

SYNTHESIS OF 3-(4-(2-(4-(2-(4-(3-CHLORO-2-HYDROXYPROPOXY)PHENYL)PROPAN-2-YL)PHENYL)PROPAN-2-YL)PHENOXY)PROPANE-1,2-DIOL (10)



To a solution of *racemic* **9** (203 mg, 0.39 mmol, 1 equiv) in acetonitrile (3 mL) was added $CeCl_3 \cdot 7H_2O$ (366 mg, 0.98 mmol, 2.5 equiv), and the mixture was refluxed for 19 h. The resulting white paste was filtered and washed with ethyl acetate, and the clear suspension was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 5% methanol in dichloromethane to 10% methanol) to provide **10** (144 mg, 71%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19-7.15 (m, 4H), 7.12 (br, 4H), 6.85-6.81 (m,

4H), 4.22-4.18 (m, 1H), 4.11-4.05 (m, 3H), 4.00 (d, J = 5.6, 2H), 3.84-3.80 (dd, J = 11.6, 3.6, 1H), 3.78-3.69 (m, 3H), 3.07 (m, 3H), 1.66 (d, J = 2.0, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 156.2, 148.0, 147.9, 144.0, 143.8, 128.1, 128.1, 126.4, 114.1, 114.1, 70.7, 70.1, 69.2, 68.7, 63.9, 46.1, 42.1, 31.0, HRMS (ESI) (*m/z*): calc'd for $C_{30}H_{37}O_5NaCl$ $[M+Na]^+$: 535.2227, found: 535.2222.

EXAMPLE 7

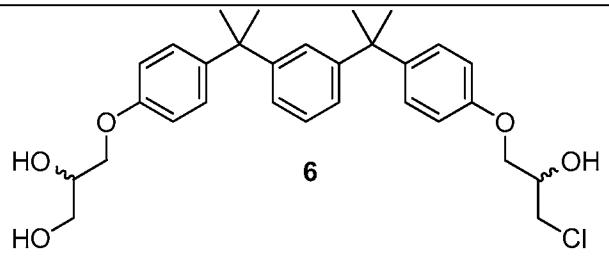
IN VITRO ACTIVITY OF SELECT COMPOUNDS

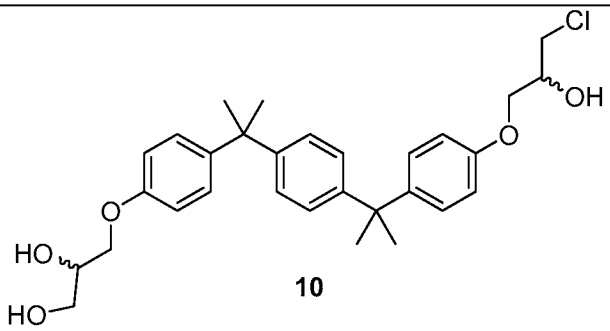
LNCaP cells were transiently cotransfected with PSA (6.1 kb)-luciferase (0.25 μg/well) in 24-well plates for 24 h prior to pre-treatment with compounds for 1 hour before the addition of synthetic androgen, R1881 (1 nM) to induce PSA production or vehicle. The total amount of plasmid DNA transfected was normalized to 0.75 μg/well by the addition of the empty vector. After 48 h of incubation with R1881, the cells were harvested, and relative luciferase activity was determined. Test compounds were added to the cells at various concentrations and activity for each treatment was normalized to the predicted maximal activity induction (in the absence of test compounds, vehicle only). Plotting of sigmoidal curves (Boltzmann Function) and IC50 calculations were done using OriginPro 8.1 Sofware (Northampton, MA, USA).

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

TABLE 3 shows the compounds tested using the above-described assays and their respective activities.

TABLE 3

COMPOUND	IC50
 **6**	1.0 μM

 10	0.6 μM

EXAMPLE 8

IN VIVO DOSE RESPONSE OF COMPOUNDS

In vivo dose response of compounds of the invention is determined according to the following procedure: Male athymic SCID-NOD mice, 6- to 8-weeks old, are inoculated subcutaneously with LNCaP cells (1 x 10^6) suspended in 75 μl of RPMI 1640 (5% FBS) and 75 μl of Matrigel (Becton Dickinson Labware) in the flank region via a 27-gauge needle under isofluorane anesthesia. Mice bearing LNCaP subcutaneous tumors are castrated when tumor volumes are approximately 100 mm^3. Seven days after castration, mice are injected intravenously by tail vein every other day for a total of 7 doses with compounds of the invention in 15% DMSO and 25.5% PEG. The experiment is complete 2 days after the last injection. Tumours are measured with calipers and their volumes calculated by the formula L x W x H x 0.5236. Tumor volume as a a function of compound dose is plotted.

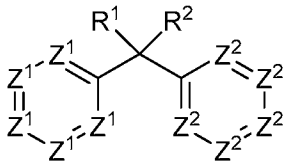
Dose reponse of comparative compounds are also determined according to the above procedure.

Although various embodiments of the invention are disclosed herein, many adaptations and modifications may 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 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 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

1. A compound having a structure of Formula I:

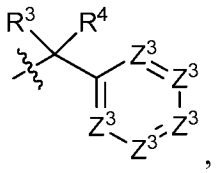


I

or a pharmaceutically acceptable salt or tautomer thereof, wherein:

at least one Z^1 is independently C-Q;

at least one Z^2 is independently C-W, wherein W is

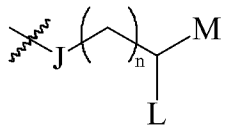


,

at least one Z^3 is independently C-T, CH, CCH_3, CF, CCl, CBr, CI, COH, CG^1, COG^1, CNH_2, $CNHG^1$, $CNG^1{}_2$, $COSO_3H$, $COPO_3H_2$, CSG^1, $CSOG^1$, or CSO_2G^1,

each remaining Z^1, Z^2 and Z^3 is, at each occurrence, independently C-T, N, CH, CCH_3, CF, CCl, CBr, CI, COH, CG^1, COG^1, CNH_2, $CNHG^1$, $CNG^1{}_2$, $COSO_3H$, $COPO_3H_2$, CSG^1, $CSOG^1$, or CSO_2G^1;

R^1, R^2, R^3 and R^4 are each independently H or a linear or branched, substituted or unsubstituted, saturated or unsaturated C_1-C_{10} alkyl, or R^1 and R^2, or R^3 and R^4 may independently together form a substituted or unsubstituted, saturated or unsaturated cyclic C_3-C_{10} alkyl or R^1 and R^2, or R^3 and R^4 may independently together form =CR″R‴, wherein R″ and R‴ are each independently a linear or branched, substituted or unsubstituted, saturated or unsaturated C_1-C_{10} alkyl, aryl or aralkyl;

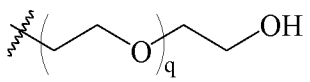
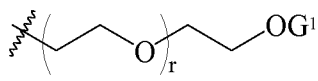
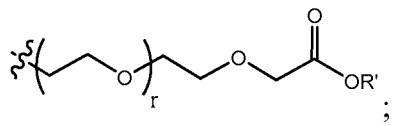
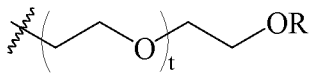
Q is  ;

J is G^1, O, CH_2, CHG^1, $CG^1{}_2$, S, NH, NG^1, SO, SO_2, or NR;

M is H, F, Cl, Br, CH_2OH, CH_2OD, CH_2OG^1, CH_2F, CH_2Cl, $CHCl_2$, CCl_3, CH_2Br, $CHBr_2$, CBr_3 or C≡CH;

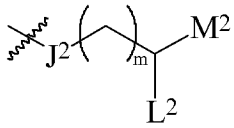
L is H or A-D;

A is O, S, NH, NG^1, N^+H_2 or N^+HG^1;

D is, at each occurrence, independently H, G^1, R,  ,  ,  ;  or a moiety from TABLE 1;

each of q, r and t may independently be 0, 1, 2, 3, 4, 5, 6 or 7;

n is 0, 1, 2, 3, 4, 5, 6, 7 or 8;

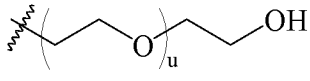
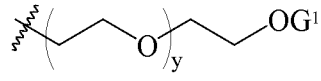
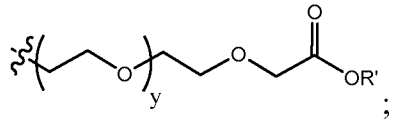
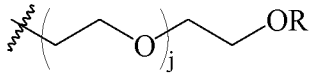
T is, at each occurrence, independently  ;

J^2 is, at each occurrence, independently G^1, O, CH_2, CHG^1, $C(G^1)_2$, S, NH, NG^1, SO, SO_2, or NR;

M^2 is, at each occurrence, independently H, CH_3, F, Cl, Br, CH_2F , CH_2Cl, $CHCl_2$, CCl_3, CH_2Br, $CHBr_2$, CBr_3, CH_2OH, CH_2OD^2, CH_2OJ'', G^1, CH_2OG^1, CH_2OR, $CH_2OG^1OG^{1\prime}$, $G^1OG^{1\prime}$, $G^1OG^{1\prime}OG^{1\prime\prime}$, CH_2SG^1, CH_2NH_2, CH_2NHG^1, $CH_2NG^1{}_2$, or C≡CH;

L^2 is, at each occurrence, independently H or A^2-D^2;

A^2 is, at each occurrence, independently O, S, SO, SO2, NH, NG^1, N^+H_2, or N^+HG^1;

D^2 is, at each occurrence, independently H, G^1, R,  ,  ,  ;  or a moiety selected from TABLE 1;

each of u, y and j are, at each occurrence, independently 0, 1, 2, 3, 4, 5, 6 or 7;

m is, at each occurrence, independently 0, 1, 2, 3, 4, 5, 6, 7 or 8;

J″ and J‴ are, at each occurrence, independently a moiety selected from TABLE 1;

G^1, $G^{1\prime}$ and $G^{1\prime\prime}$ are, at each occurrence, independently a linear or branched, aromatic cyclic or non-aromatic cyclic, substituted or unsubstituted, saturated

or unsaturated C_1-C_{10} alkyl, wherein the optional substituents for the C_1-C_{10} alkyl are oxo, CH_2CO_2R', OJ‴, COOH, R^1, OH, OR^1, F, Cl, Br, I, NH_2, NHR^1, $N(R^1)_2$, CN, SH, SR^1, SO_3H, SO_3R^1, SO_2R^1, OSO_3R^1, OR^2, CO_2R^1, $CONH_2$, $CONHR^1$, $CONHR^2$, $CON(R^1)_2$, NHR^2, OPO_3H_3, $CONR^1R^2$, NR^1R^2 or NO_2;

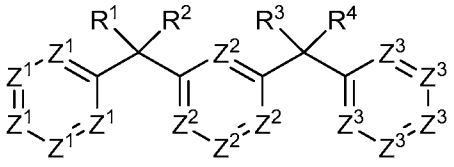
each R' is independently H, linear or branched, aromatic cyclic or non-aromatic cyclic, substituted or unsubstituted, saturated or unsaturated C_1-C_{10} alkyl or a metal counter ion, wherein the metal counter ion is Li, Na, K, Mg or Ca;

each R^1 is independently unsubstituted C_1-C_{10} alkyl; and

each R and R^2 are independently C_1-C_{10} acyl.

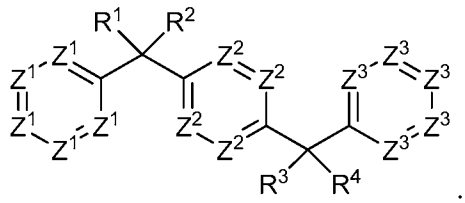
2. The compound of claim 1, wherein in at least one Z^3 is independently C-T.

3. The compound of any of claims 1 or 2, wherein the compound has a structure of Formula II or III:



II

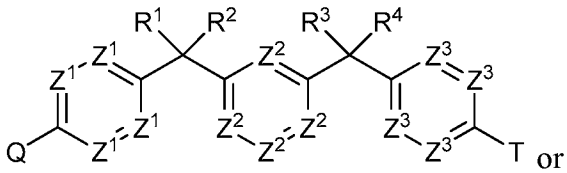
or



III

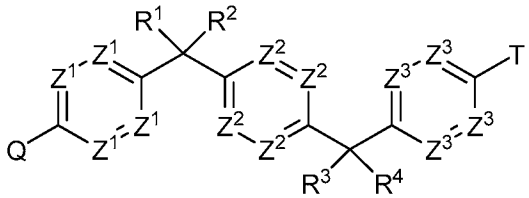
.

4. The compound of claim 1, wherein the compound has a structure of Formula IV or V:



IV

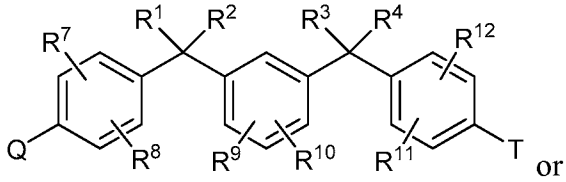
or



V

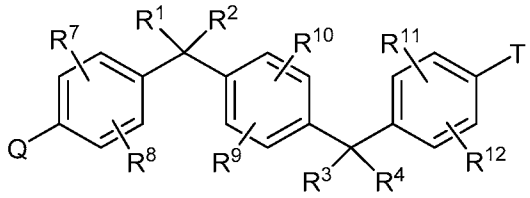
.

5. The compound of claim 1, wherein the compound has a structure of Formula VI or VII:



or

VI

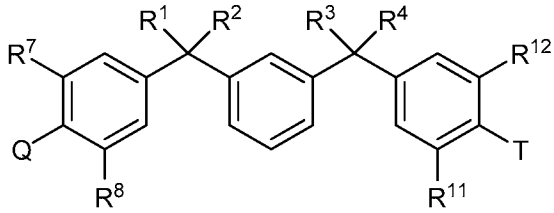


VII

wherein:

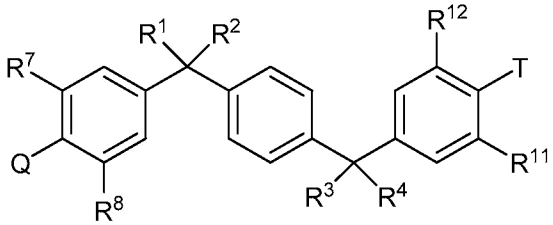
R^7, R^8, R^9, R^{10}. R^{11} and R^{12} are each independently hydrogen, halo, or linear or branched, substituted or unsubstituted, saturated or unsaturated C_1-C_{10} alkyl.

6. The compound of claim 1, wherein the compound has a structure of Formula VIII or IX:



or

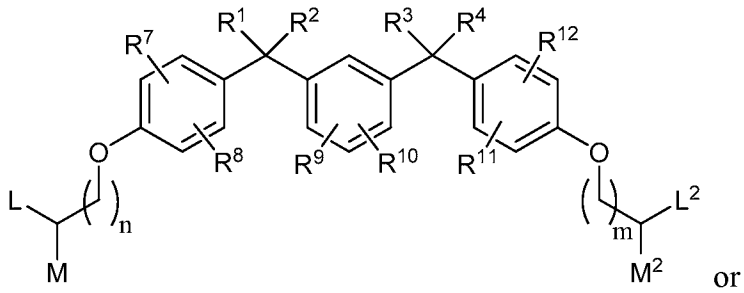
VIII



.

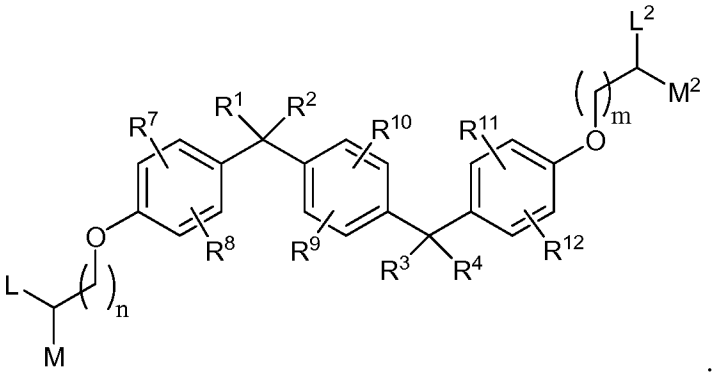
IX

7. The compound of claim 1, wherein the compound has a structure of Formula X or XI:



or

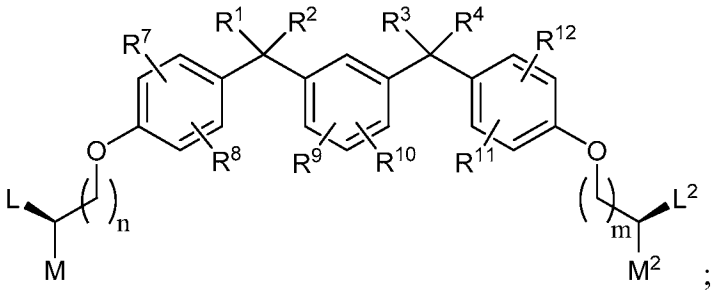
X



.

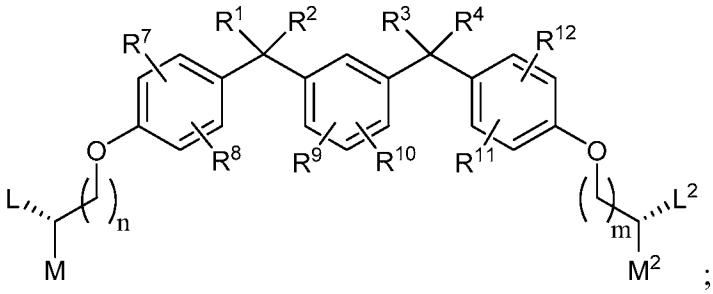
XI

8. The compound of claim 1, wherein the compound has a structure of Formula Xa, Xb, Xc, Xd, XIa, XIb, XIc or XId:



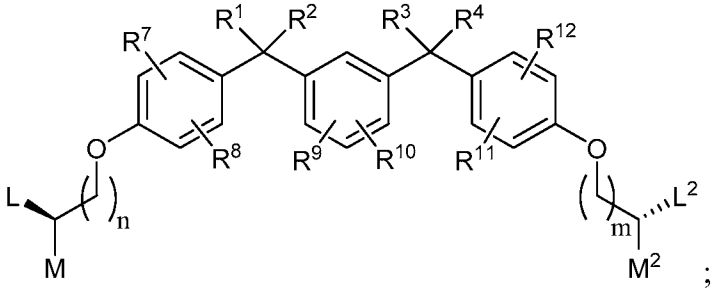
;

Xa



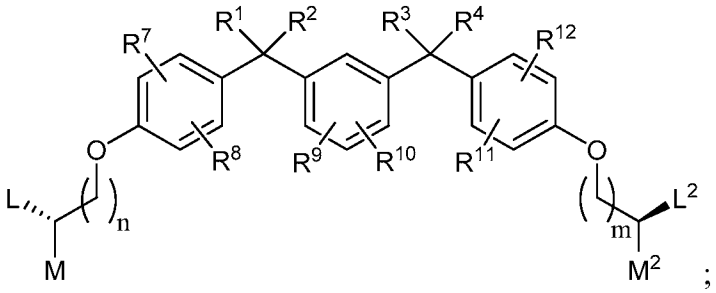
;

Xb



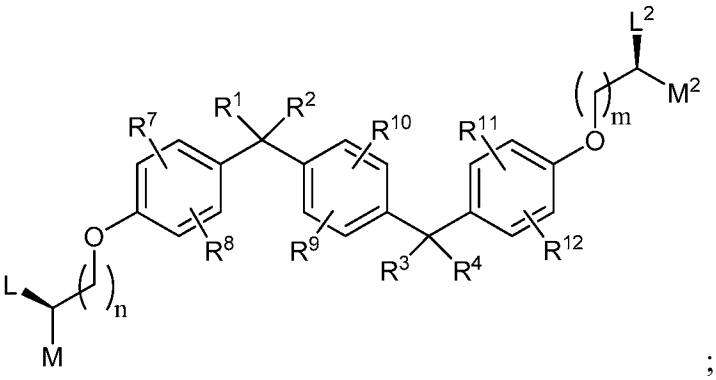
;

Xc



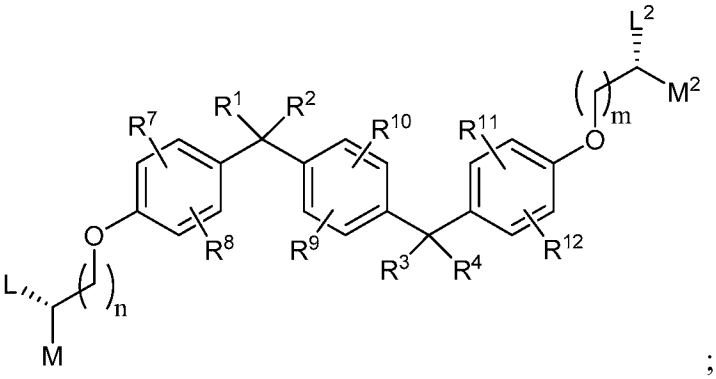
;

Xd



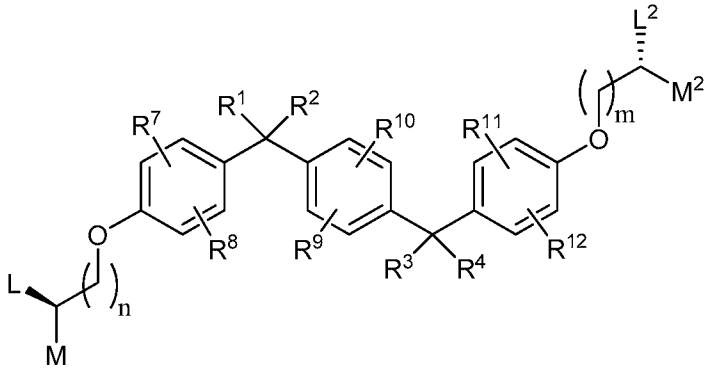
;

XIa



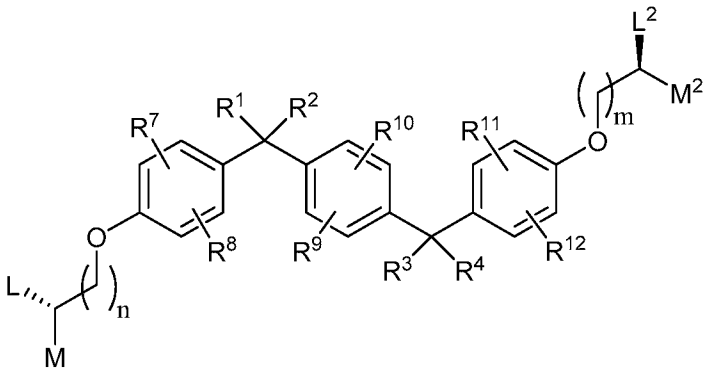
;

XIb



; or

XIc



.

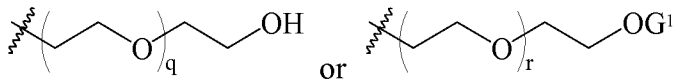
XId

9. The compound of any one of claims 1 to 6, wherein J is G^1, O, CH_2, CHG^1, CG^1_2, NH, SO, or NR.

10. The compound of any one of claims 1 to 6, wherein J is O.

11. The compound of any one of claims 1 to 8, wherein M is Cl, Br, CH_2OH, CH_2OD, CH_2OG^1, CH_2F, CH_2Cl, $CHCl_2$, CCl_3, CH_2Br, $CHBr_2$, CBr_3, or C≡CH.

12. The compound of any one of claims 1 to 8, wherein M is CH_2OH, CH_2F, C≡CH, $CH_2OCH_2C{\equiv}CH$, CH_2O-*n*-butyl, or CH_2OD, wherein D is



.

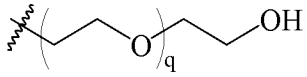
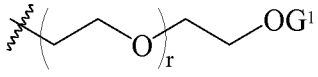
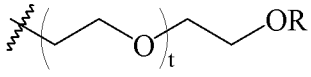
13. The compound of any one of claims 1 to 8, wherein M is CH_2OH.

14. The compound of any one of claims 1 to 8, wherein M is H.

15. The compound of any one of claims 1 to 14, wherein L is H.

16. The compound of any one of claims 1 to 14, wherein L is A-D.

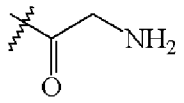
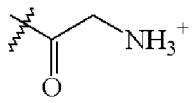
17. The compound of any one of claims 1 to 14, wherein A is O.

18. The compound of any one of claims 16 or 17, wherein D is H, R,  ,  ,  , or a moiety from TABLE 1; and each of q, r and t is independently 0, 1, 2, 3, 4, 5, 6 or 7.

19. The compound of any one of claims 16 or 17, wherein D is H.

20. The compound of any one of claims 16 or 17, wherein D is R.

21. The compound of any one of claims 16 or 17, wherein D is a moiety selected from TABLE 1.

22. The compound of claim 21, wherein the moiety from TABLE 1 is  or  .

23. The compound of any one of claims 1 to 22, wherein n is 0.

24. The compound of any one of claims 1 to 22, wherein n is 1, 2, 3, 4, or 5.

25. The compound of any one of claims 1 to 22, wherein n is 1.

26. The compound of any one of claims 1 to 6, wherein J^2 is G^1, O, CH_2, CHG^1, CG^1_2, NH, SO, or NR.

27. The compound of any one of claims 1 to 6, wherein J^2 is O.

28. The compound of any one of claims 1 to 27, wherein M^2 is H, CH_2F, CH_2Cl, CH_2Br, CH_2OH, CH_2OJ'', CH_2OG^1, or C≡CH.

29. The compound of any one of claims 1 to 27, wherein M^2 is CH_2F.

30. The compound of any one of claims 1 to 27, wherein M^2 is CH_2Cl.

31. The compound of any one of claims 1 to 27, wherein M^2 is CH_2Br.

32. The compound of any one of claims 1 to 27, wherein M^2 is CH_2OH.

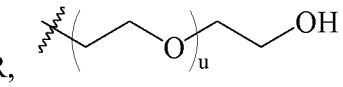
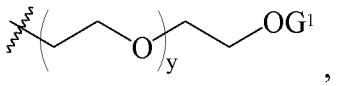
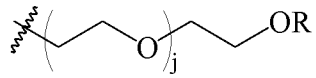
33. The compound of any one of claims 1 to 27, wherein M^2 is H.

34. The compound of any one of claims 1 to 27, wherein M^2 is C≡CH.

35. The compound of any one of claims 1 to 34, wherein L^2 is H.

36. The compound of any one of claims 1 to 34, wherein L^2 is A^2-D^2.

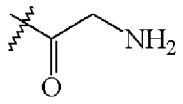
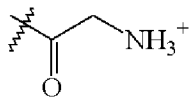
37. The compound of claim 36, wherein A^2 is O .

38. The compound of any one of claims 36 or 37, wherein D^2 is H, R,  ,  ,  , or a moiety from TABLE 1; and each of u, y and j is independently 0, 1, 2, 3, 4, 5, 6 or 7.

39. The compound of any one of claims 36 or 37, wherein D^2 is H.

40. The compound of any one of claims 36 or 37, wherein D^2 is R.

41. The compound of any one of claims 36 or 37, wherein D^2 is a moiety from TABLE 1.

42. The compound of claim 41, wherein the moiety from TABLE 1 is  or  .

43. The compound of any one of claims 1 to 42, wherein m is 0.

44. The compound of any one of claims 1 to 42, wherein m is 1, 2, 3, 4, or 5.

45. The compound of any one of claims 1 to 42, wherein m is 1.

46. The compound of any one of claims 1 to 8, wherein M is CH_2OH and L is OH.

47. The compound of any one of claims 1 to 8, wherein M^2 is CH_2Cl and L is OH.

48. The compound of any one of claims 1 to 8, wherein M is CH_2OH, M^2 is CH_2Cl, L is OH and L^2 is OH.

49. The compound of claim 48, wherein n and m are each 1.

50. The compound of any one of claims 1 to 49, wherein at least one of R^1, R^2, R^3 or R^4 is methyl.

51. The compound of any one of claims 1 to 49, wherein each of R^1, R^2, R^3 and R^4 is methyl.

52. The compound of any one of claims 1 to 49, wherein at least one of R^1, R^2, R^3 or R^4 is hydrogen.

53. The compound of any one of claims 1 to 49, wherein each of R^1, R^2, R^3 and R^4 is hydrogen.

54. The compound of any one of claims 1 to 49, wherein R^1 and R^2 or R^3 and R^4 join to form substituted or unsubstituted cyclohexyl.

55. The compound of any one of claims 1 to 49, wherein each of R^1 and R^2 and R^3 and R^4 join to form substituted or unsubstituted cyclohexyl.

56. The compound of any one of claims 5 to 55, wherein at least one of R^7, R^8, R^9, R^{10}, R^{11} or R^{12} is hydrogen.

57. The compound of any one of claims 5 to 55, wherein each of R^7, R^8, R^9, R^{10}, R^{11} and R^{12} are hydrogen.

58. The compound of any one of claims 5 to 55, wherein at least one of R^7, R^8, R^9, R^{10}, R^{11} or R^{12} is methyl.

59. The compound of any one of claims 5 to 55, wherein each of R^7, R^8, R^9, R^{10}, R^{11} and R^{12} are methyl.

60. The compound of any one of claims 5 to 55, wherein each of R^7, R^8, R^9, and R^{12} are methyl.

61. The compound of any one of claims 5 to 55, wherein at least one of R^7, R^8, R^9, R^{10}, R^{11} or R^{12} is fluoro.

62. The compound of any one of claims 5 to 55, wherein each of R^7, R^8, R^9, R^{10}, R^{11} and R^{12} are fluoro.

63. The compound of any one of claims 5 to 55, wherein each of R^7, R^8, R^9, and R^{12} are fluoro.

64. The compound of any one of claims 5 to 55, wherein at least one of R^7, R^8, R^9, R^{10}, R^{11} or R^{12} is chloro.

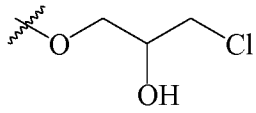
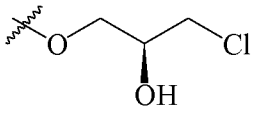
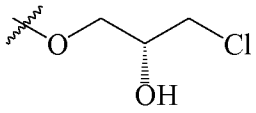
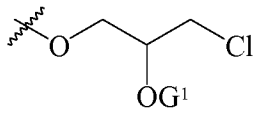
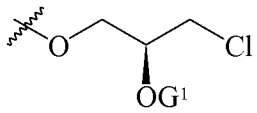
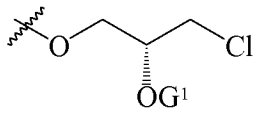
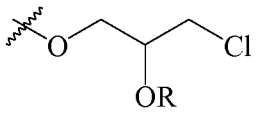
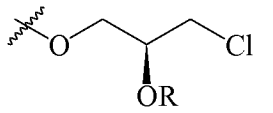
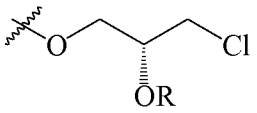
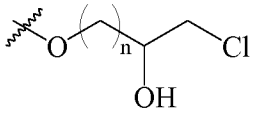
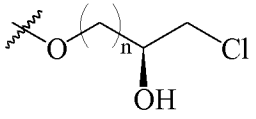
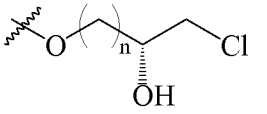
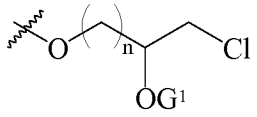
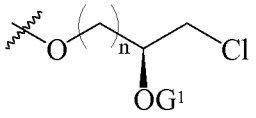
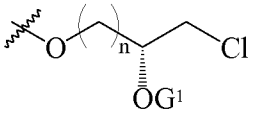
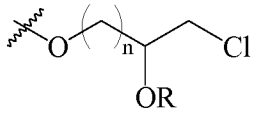
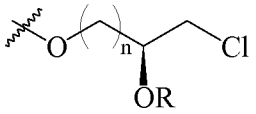
65. The compound of any one of claims 5 to 55, wherein each of R^7, R^8, R^9, R^{10}, R^{11} and R^{12} are chloro.

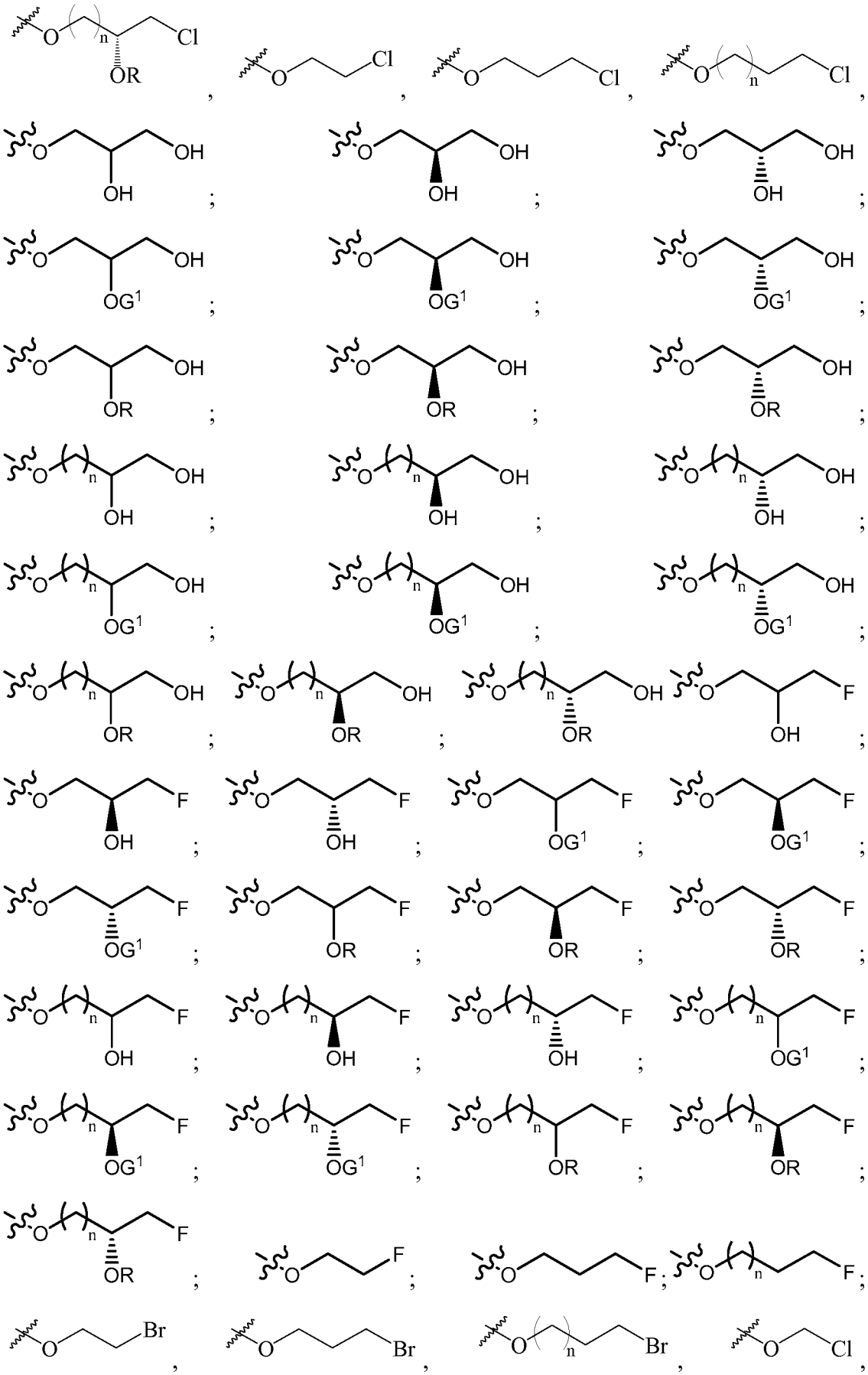
66. The compound of any one of claims 5 to 55, wherein each of R^7, R^8, R^9, and R^{12} are chloro.

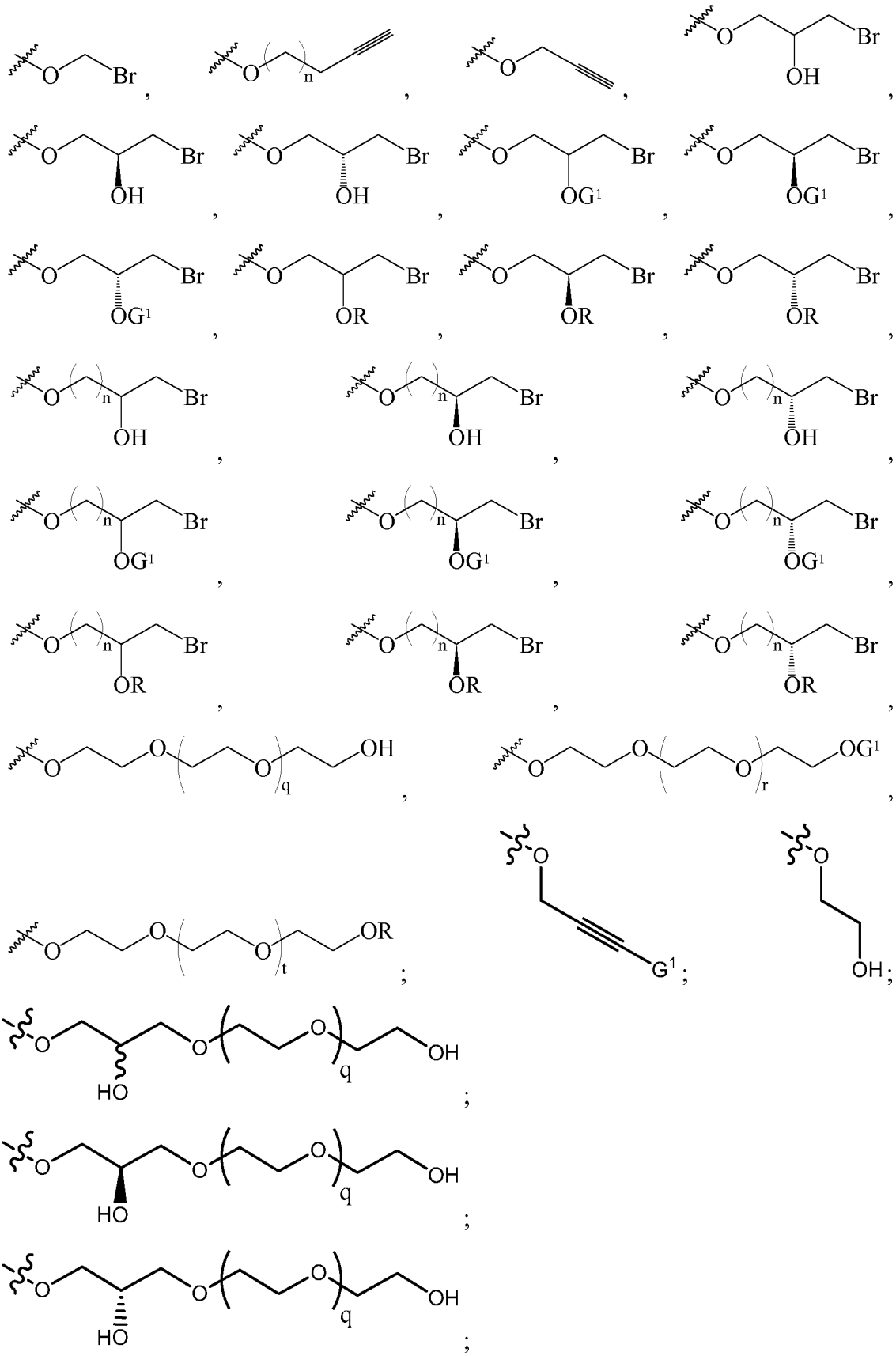
67. The compound of any one of claims 5 to 55, wherein at least one of R^7, R^8, R^9, R^{10}, R^{11} or R^{12} is bromo.

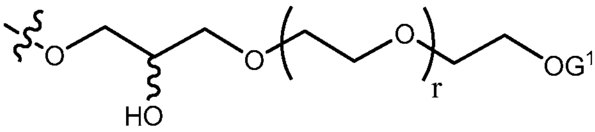
68. The compound of any one of claims 5 to 55, wherein each of R^7, R^8, R^9, R^{10}, R^{11} and R^{12} are bromo.

69. The compound of any one of claims 5 to 55, wherein each of R^7, R^8, R^9, and R^{12} are bromo.

70. The compound of any one of claims 1 to 6, wherein Q is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .



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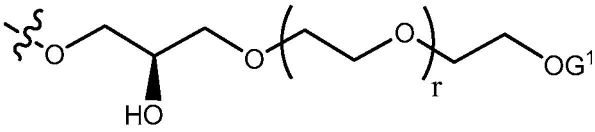
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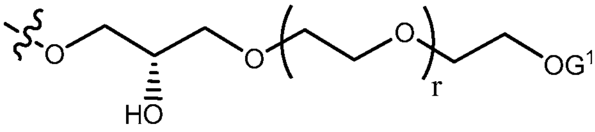
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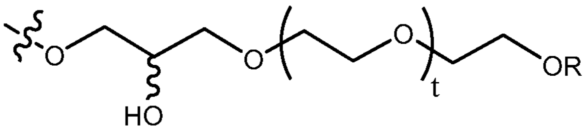
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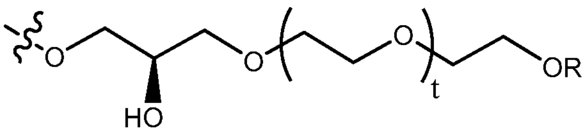
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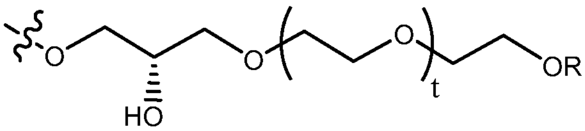
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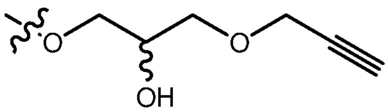
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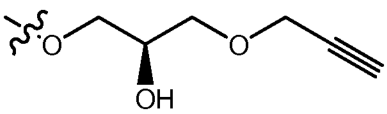
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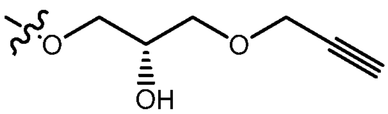
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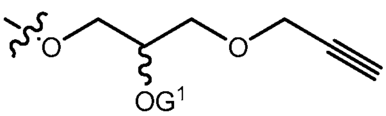
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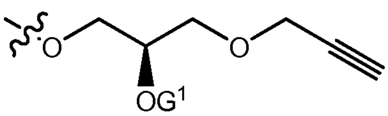
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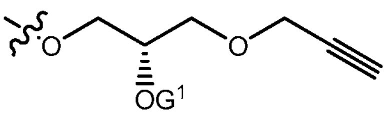
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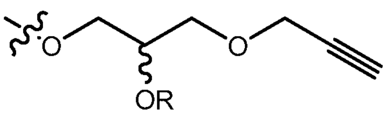
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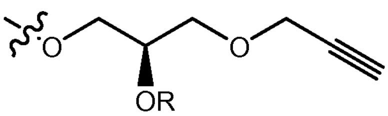
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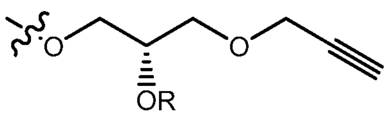
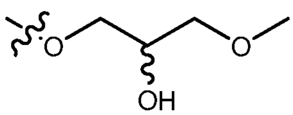
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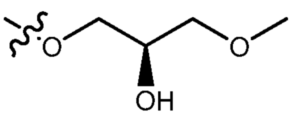
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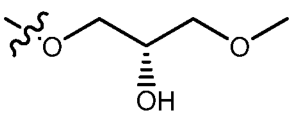
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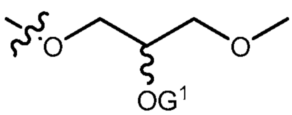
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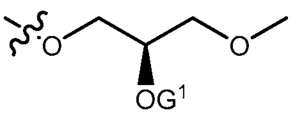
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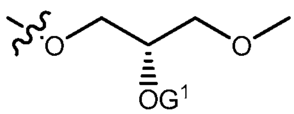
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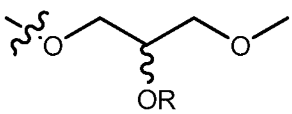
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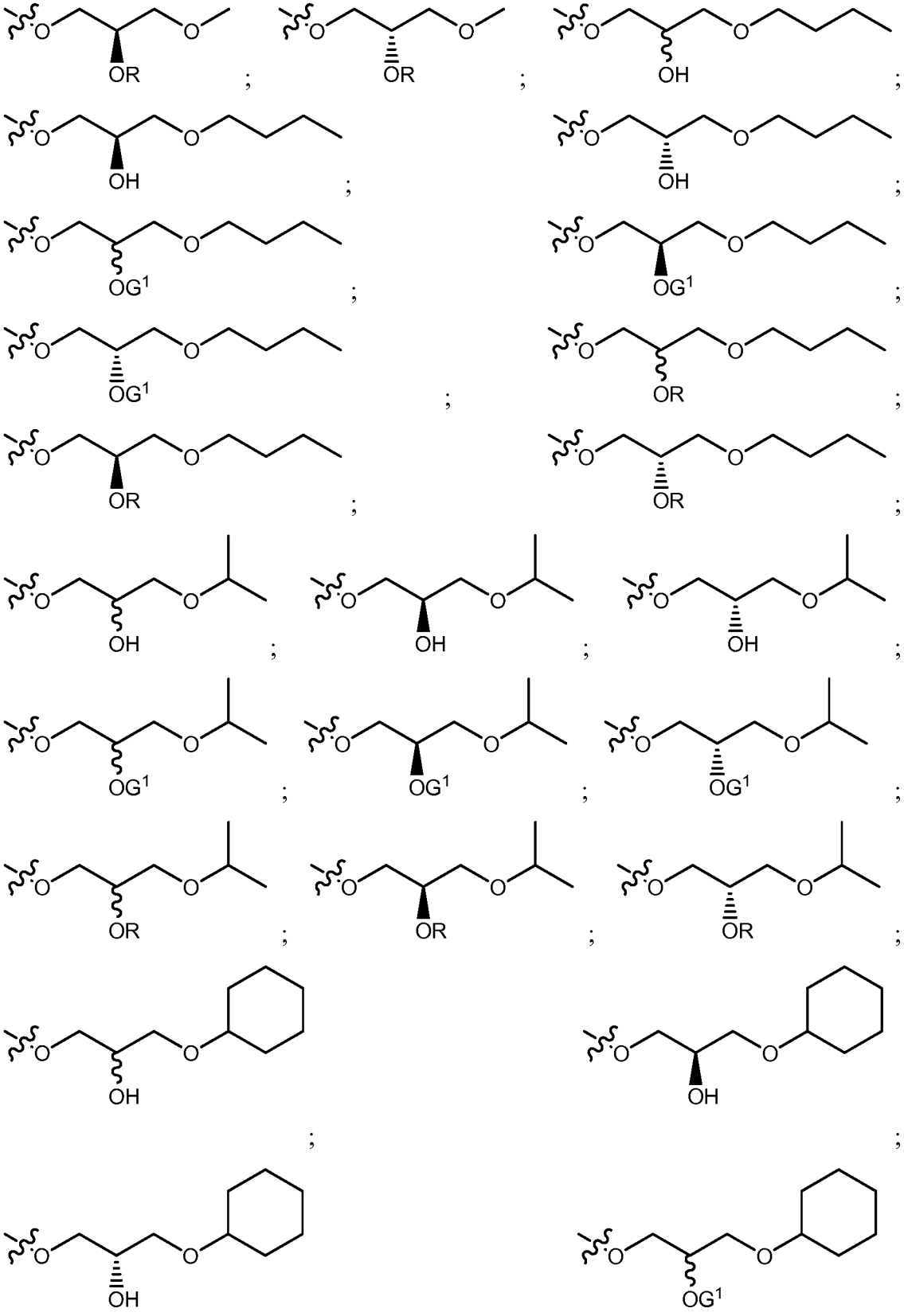

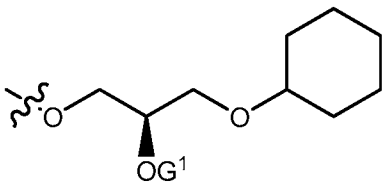
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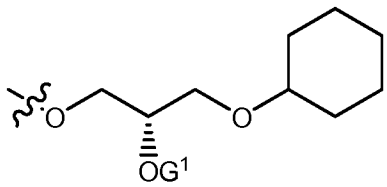
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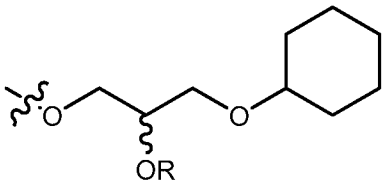
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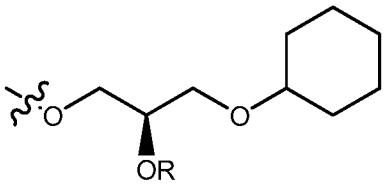
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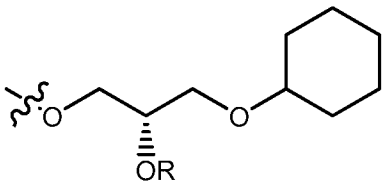
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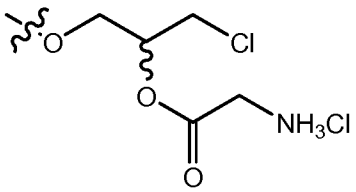
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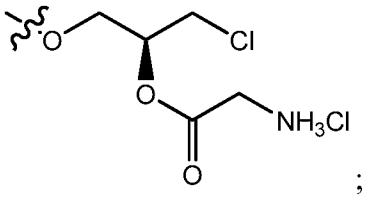
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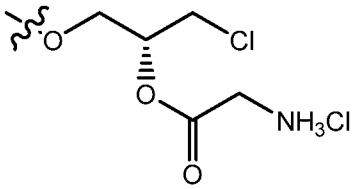
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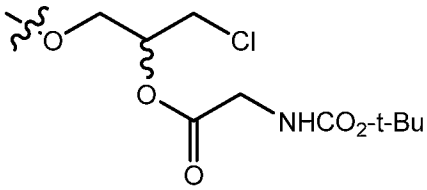
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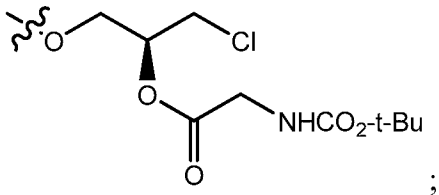
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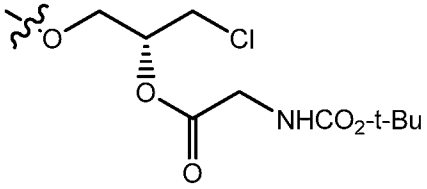
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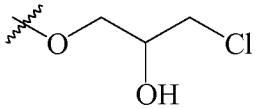
T is 
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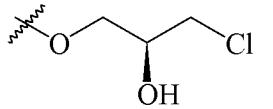
, 
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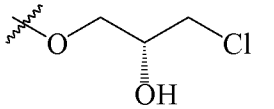
, 
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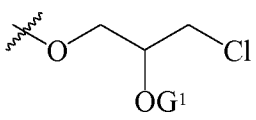
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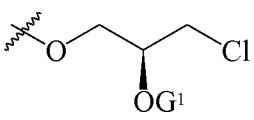
, 
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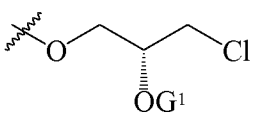
, 
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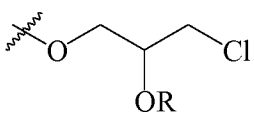
, 
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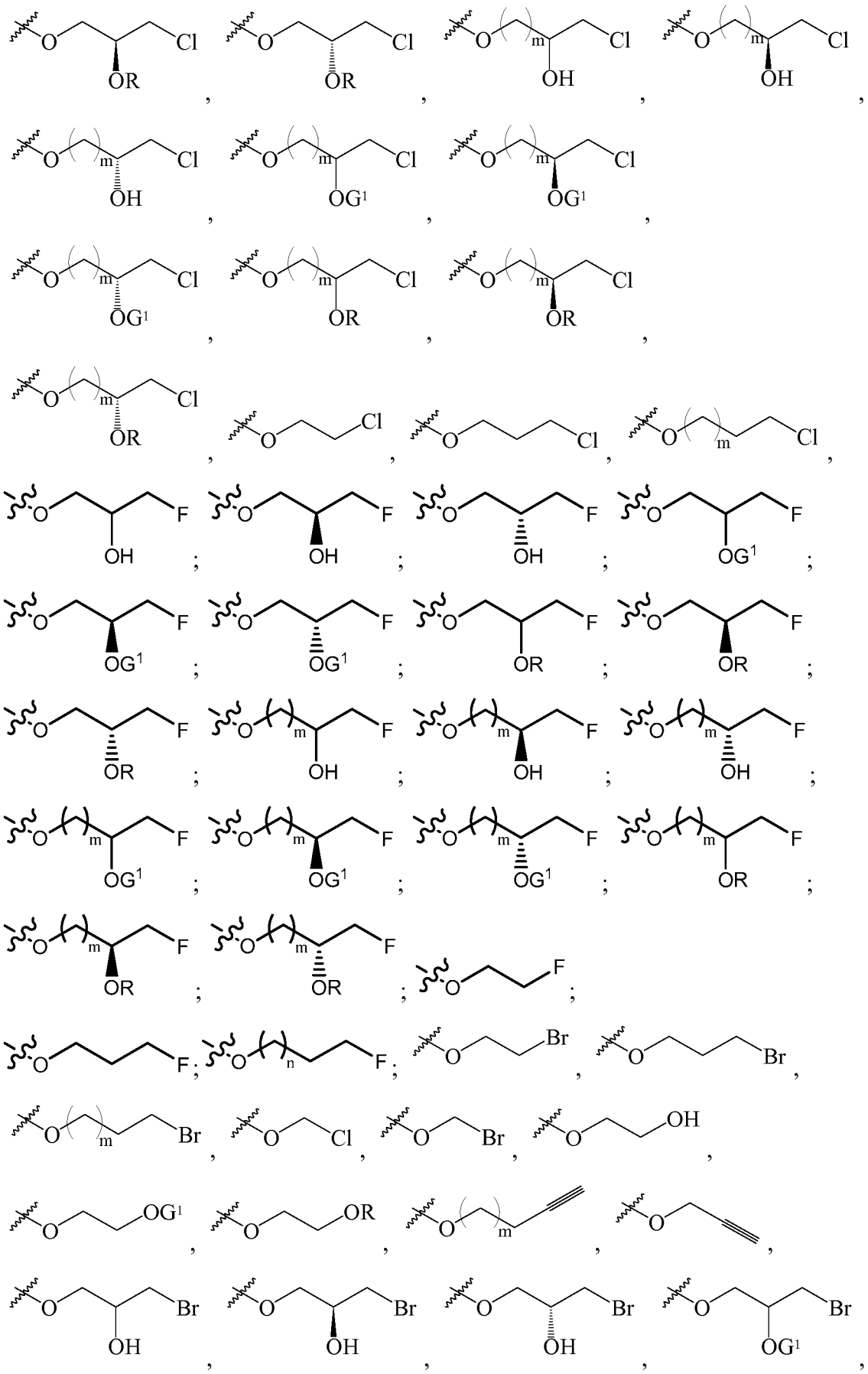

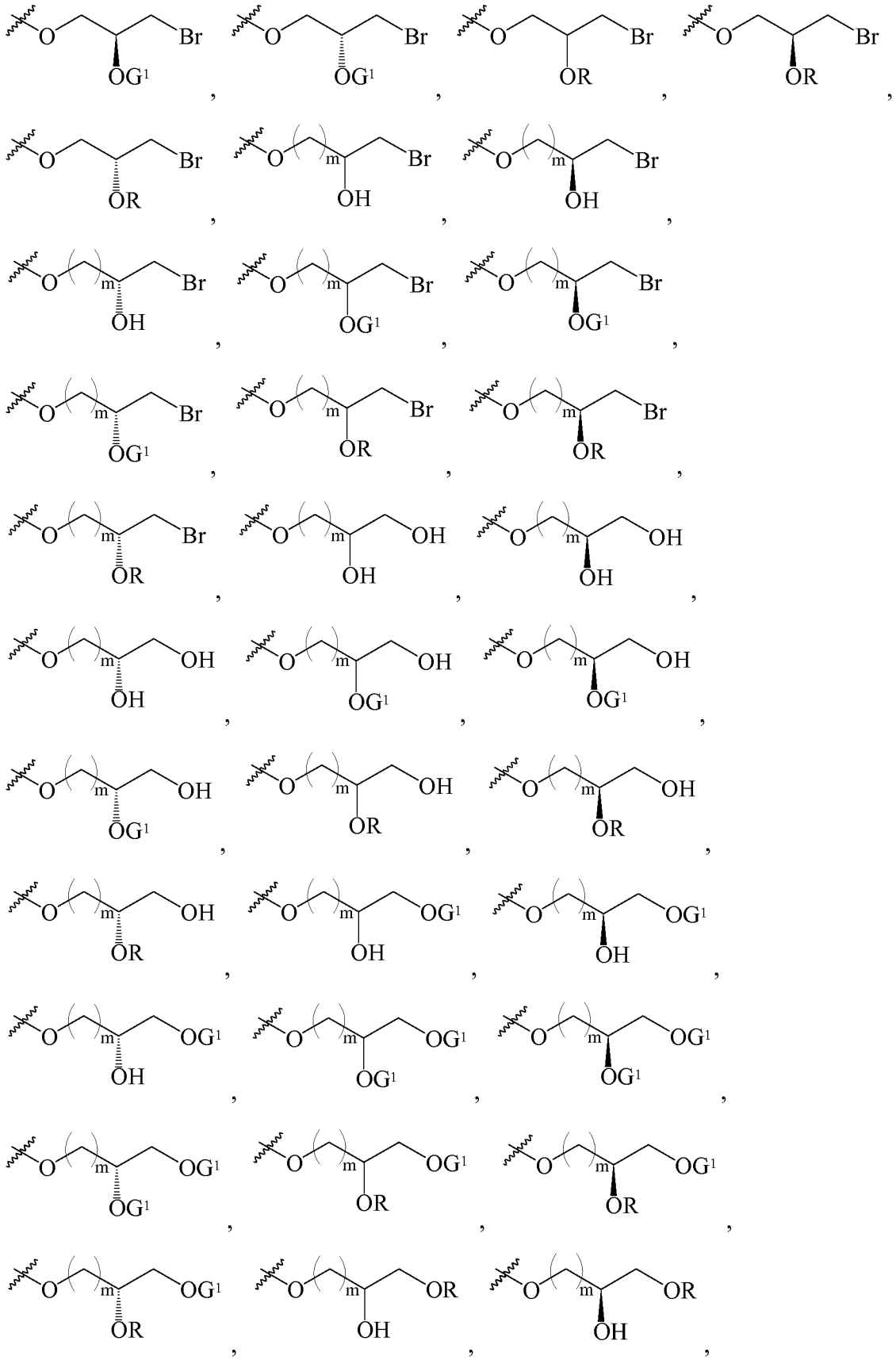

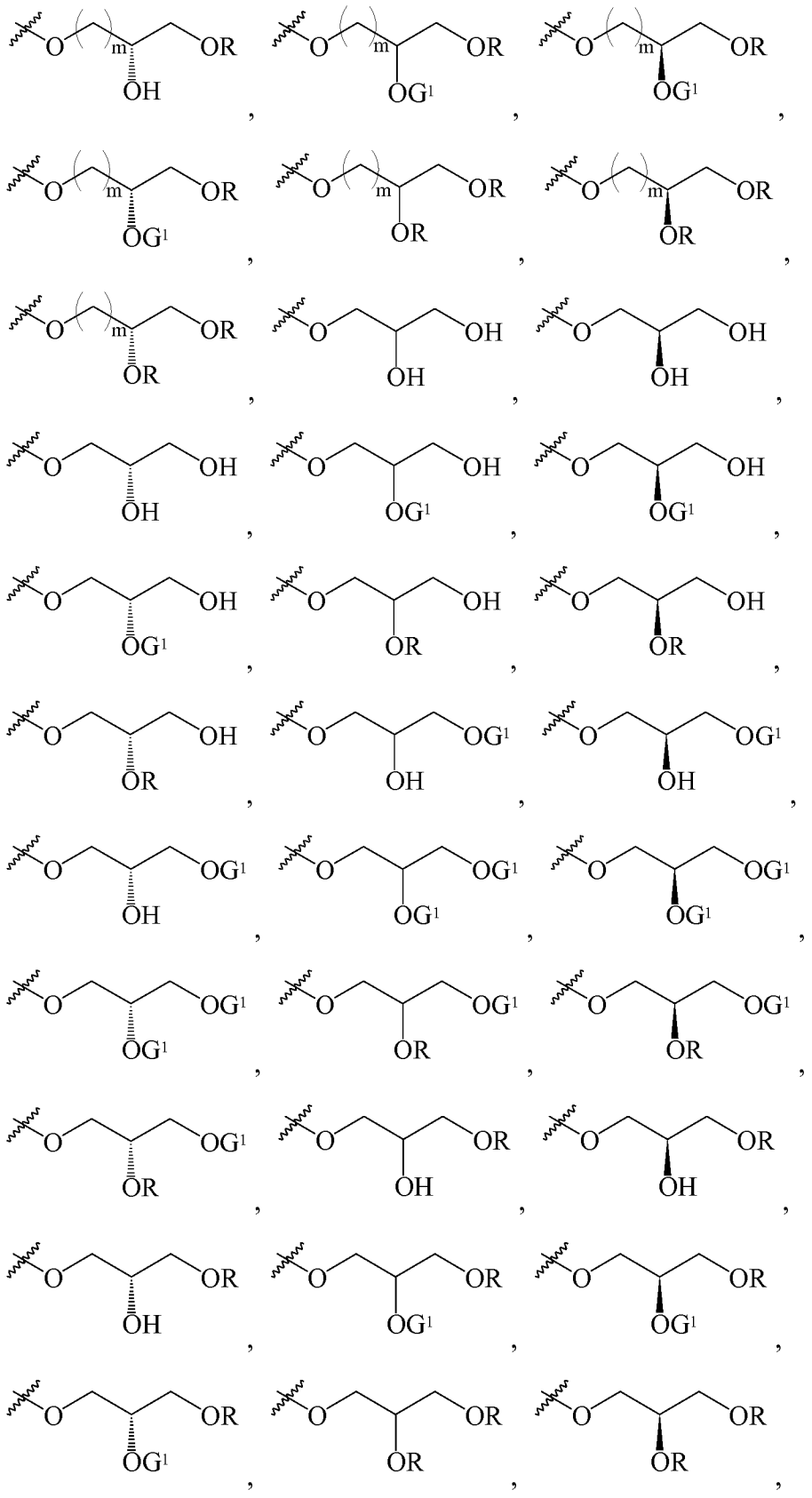

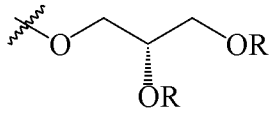
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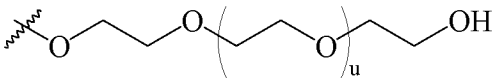
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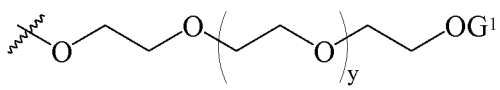
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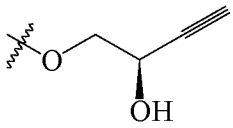
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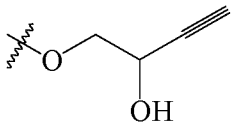
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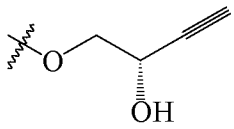
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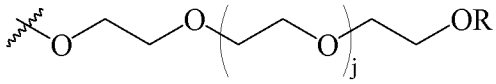
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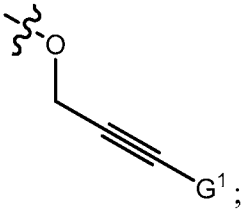
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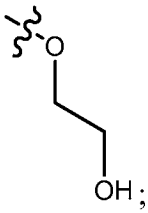
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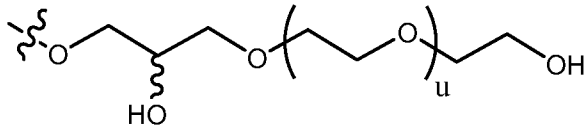
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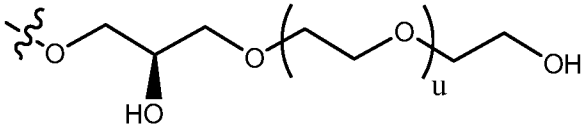
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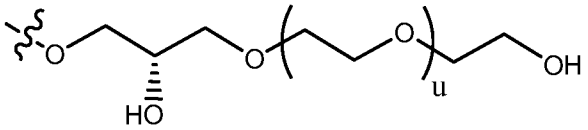
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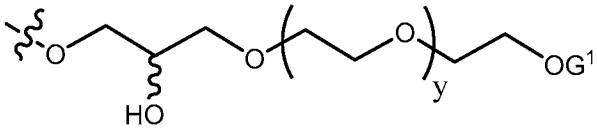
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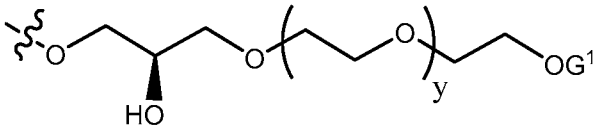
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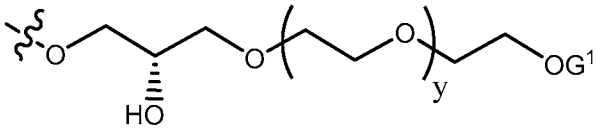
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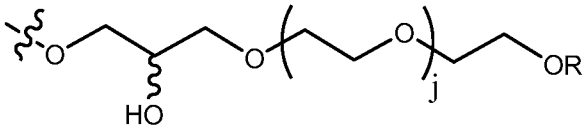
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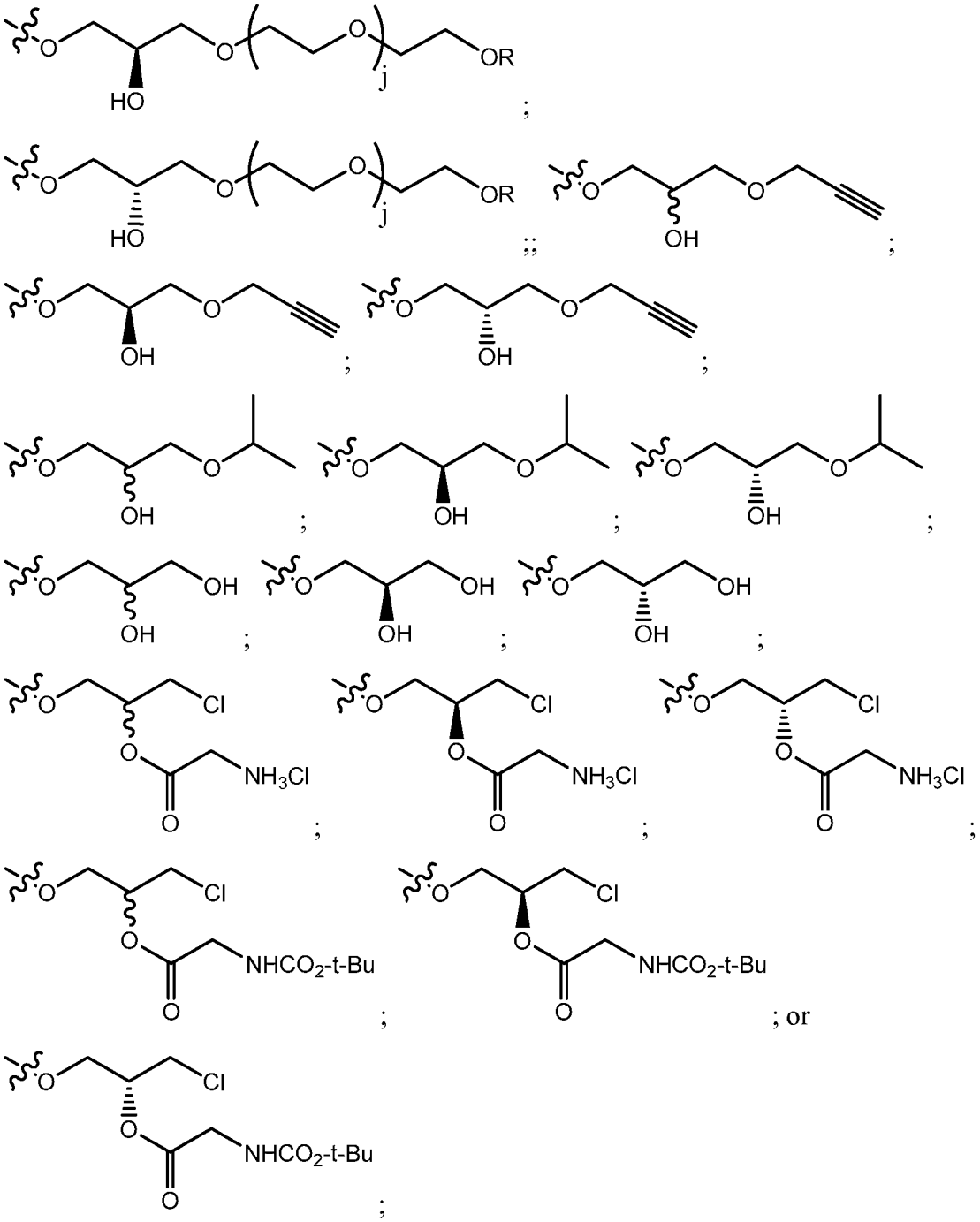


n is 0, 1, 2, 3, 4, 5, 6, 7 or 8;

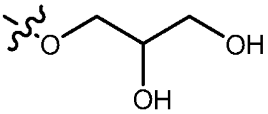
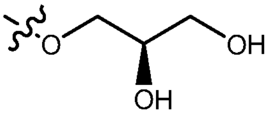
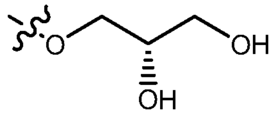
each of q, r, and t is independently 0, 1, 2, 3, 4, 5, 6 or 7;

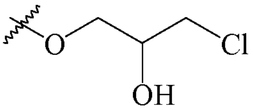
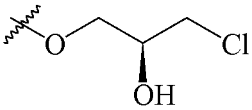
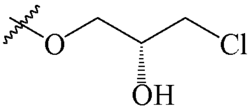
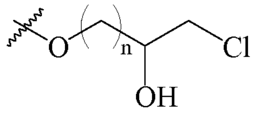
m is 0, 1, 2, 3, 4, 5, 6, 7 or 8;

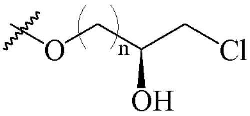
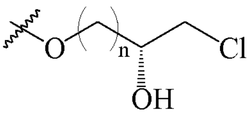
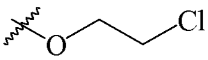
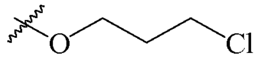
each of u, j and y is independently 0, 1, 2, 3, 4, 5, 6 or 7;

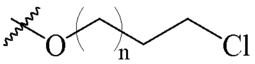
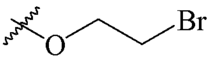
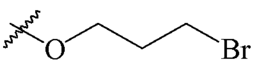
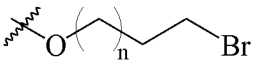
each G^1 is independently linear or branched, substituted or unsubstituted, saturated or unsaturated C_1-C_{10} alkyl, wherein the optional substituents are selected

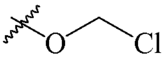
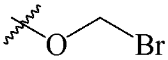
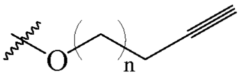
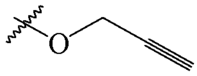
from oxo, OJ‴, COOH, OH, F, Cl, Br, I, NH_2, CN, SH, SO_3H, $CONH_2$, OPO_3H_3 and NO_2.

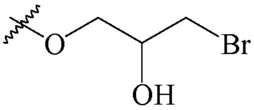
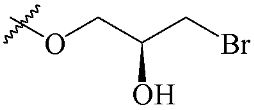
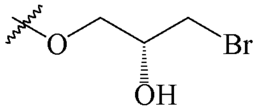
71. The compound of any one of claims 1 to 6, wherein Q is  ;  ;  ;

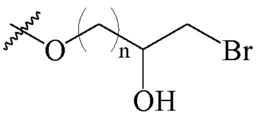
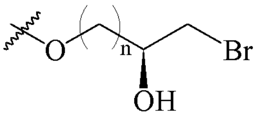
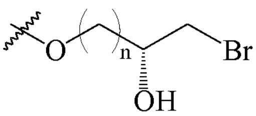
 ,  ,  ,  ,

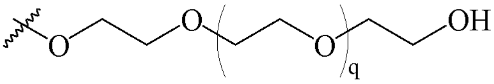
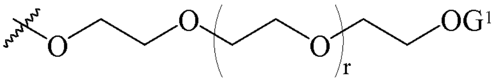
 ,  ,  ,  ,

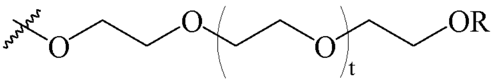
 ,  ,  ,  ,

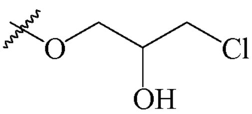
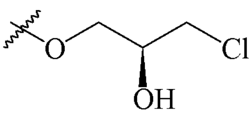
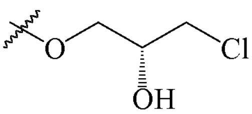
 ,  ,  ,  ,

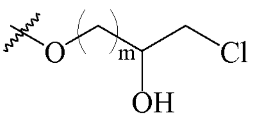
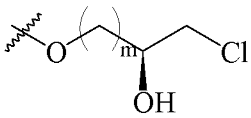
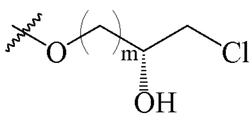
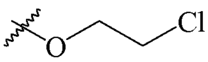
 ,  ,  ,

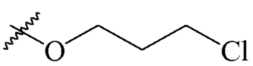
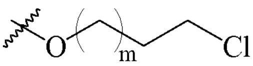
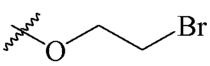
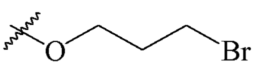
 ,  ,  ,

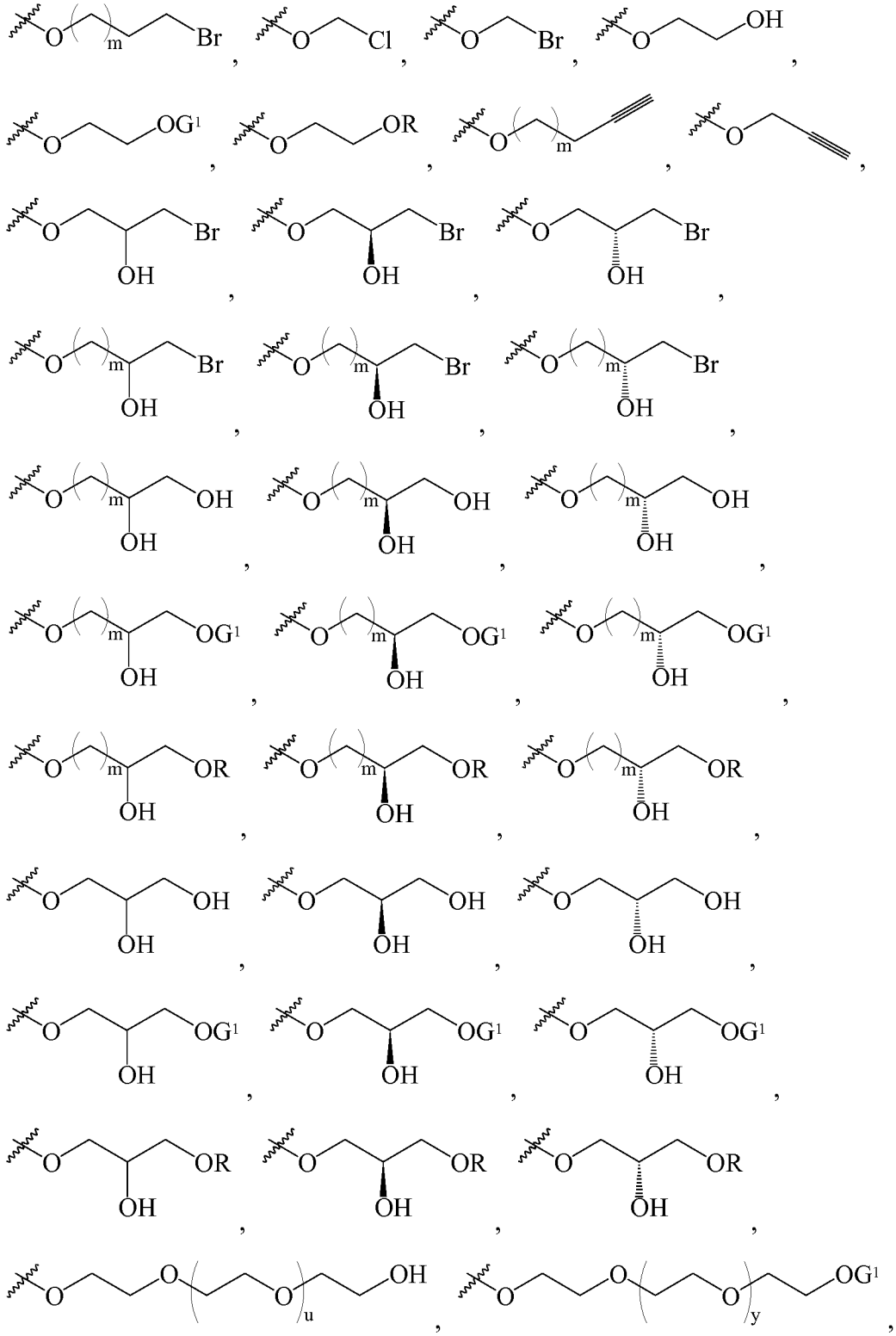
 ,  , or

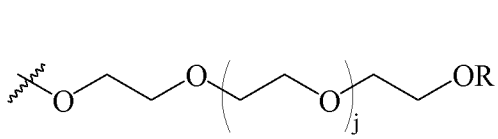
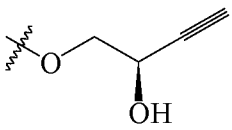
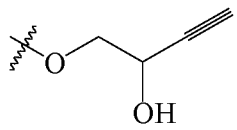
 ;

T is  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

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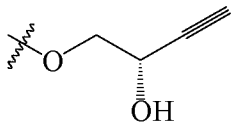

;

n is 0, 1, 2, 3, 4, 5, 6, 7 or 8;

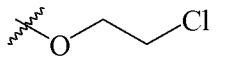
each of q, r, and t is independently 0, 1, 2, 3, 4, 5, 6 or 7;

m is 0, 1, 2, 3, 4, 5, 6, 7 or 8;

each of u, j and y is independently 0, 1, 2, 3, 4, 5, 6 or 7;

each G^1 is independently linear or branched, substituted or unsubstituted, saturated or unsaturated C_1-C_{10} alkyl, wherein the optional substituents are selected from oxo, OJ‴, COOH, OH, F, Cl, Br, I, NH_2, CN, SH, SO_3H, $CONH_2$, OPO_3H_3, and NO_2.

72. The compound of any one of claims 1 to 6, wherein Q is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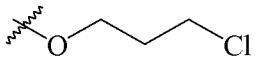
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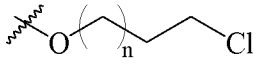
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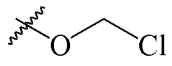
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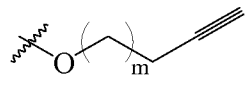
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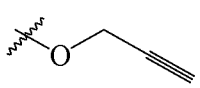
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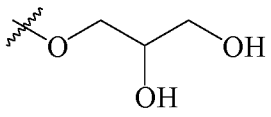
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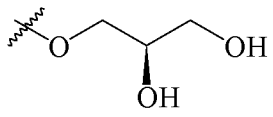
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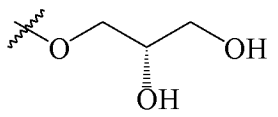
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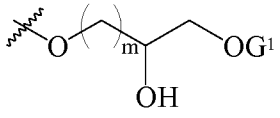
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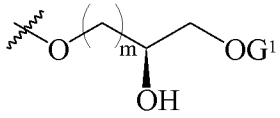
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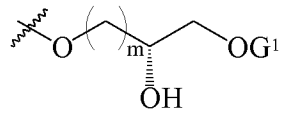
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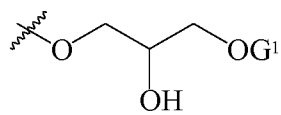
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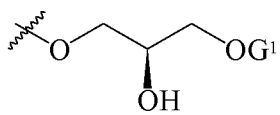
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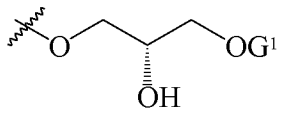
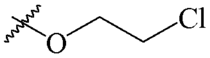
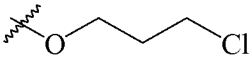
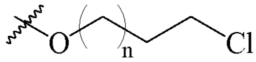
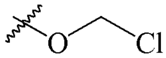

;

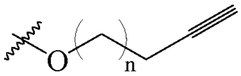
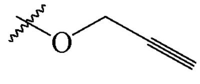
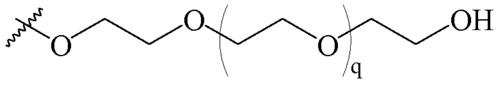
n is 0, 1, 2, 3, 4, 5, 6, 7 or 8;

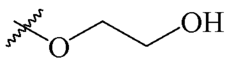
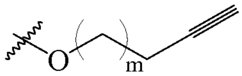
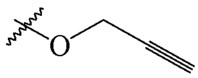
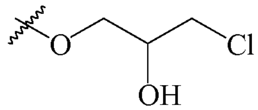
m is 0, 1, 2, 3, 4, 5, 6, 7 or 8; and

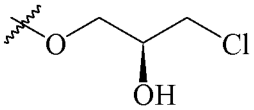
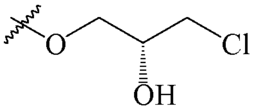
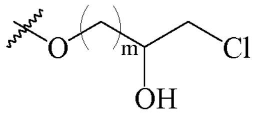
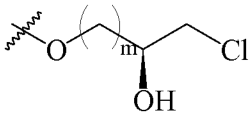
each G^1 is independently linear or branched, substituted or unsubstituted, saturated or unsaturated C_1-C_{10} alkyl, wherein the optional substituents are selected from oxo, OJ‴, COOH, OH, F, Cl, Br, I, NH_2, CN, SH, SO_3H, $CONH_2$, OPO_3H_3, and NO_2.

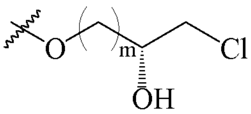
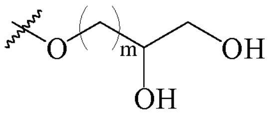
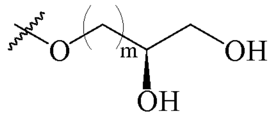
73. The compound of any one of claims 1 to 6, wherein Q is

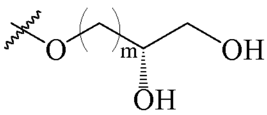
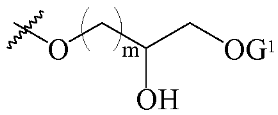
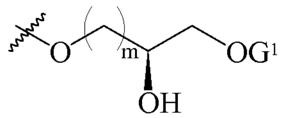
 ,  ,  ,  ,

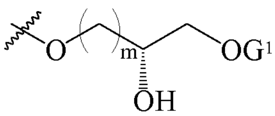
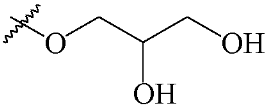
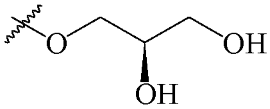
 ,  , or  ; T

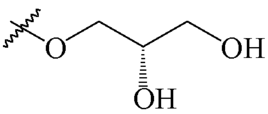
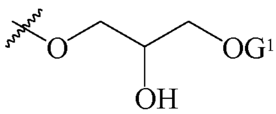
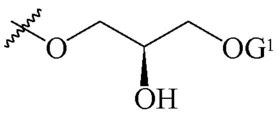
is  ,  ,  ,  ,

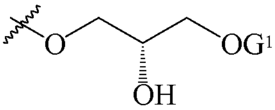
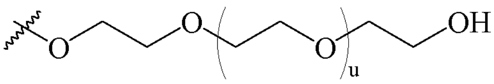
 ,  ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 , or  ;

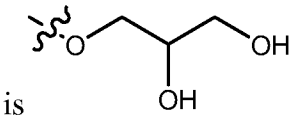
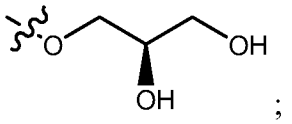
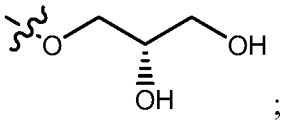
n is 0, 1, 2, 3, 4, 5, 6, 7 or 8;

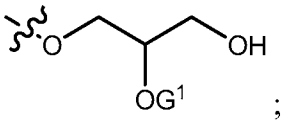
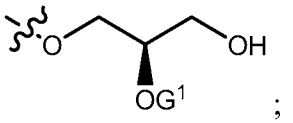
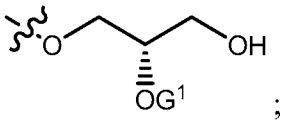
q is 0, 1, 2, 3, 4, 5, 6 or 7;

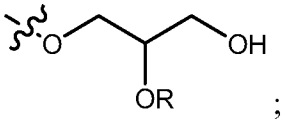
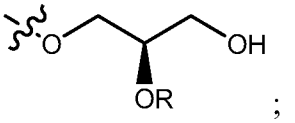
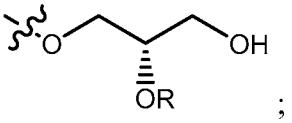
m is 0, 1, 2, 3, 4, 5, 6, 7 or 8;

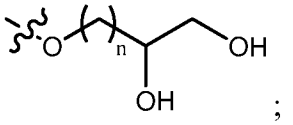
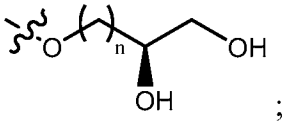
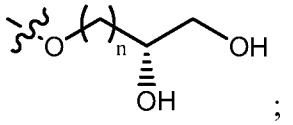
u is 0, 1, 2, 3, 4, 5, 6 or 7; and

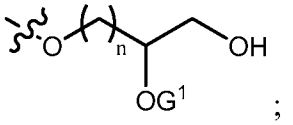
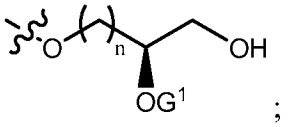
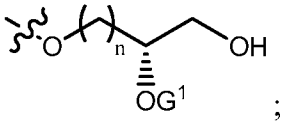
each G^1 is independently linear or branched, substituted or unsubstituted, saturated or unsaturated C_1-C_{10} alkyl, wherein the optional substituents are selected from oxo, OJ‴, COOH, OH, F, Cl, Br, I, NH_2, CN, SH, SO_3H, $CONH_2$, OPO_3H_3, and NO_2.

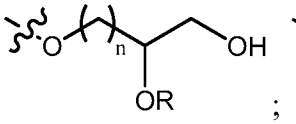
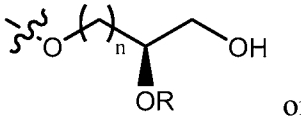
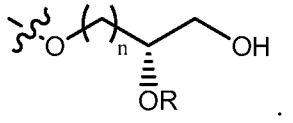
74. The compound of any one of claims 1 to 6, wherein q is  ;  ;  ;

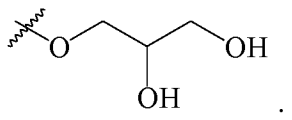
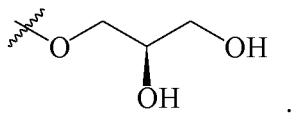
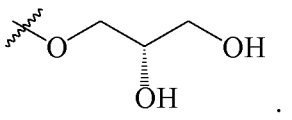
 ;  ;  ;

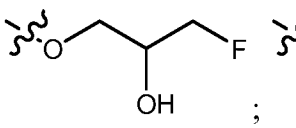
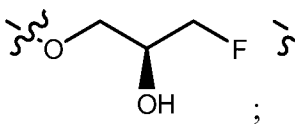
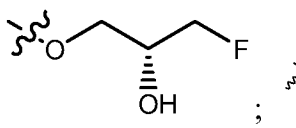
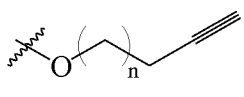
 ;  ;  ;

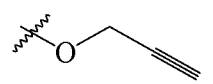
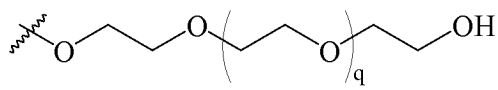
 ;  ;  ;

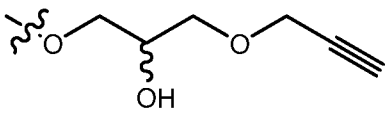
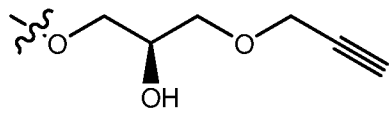
 ;  ;  ;

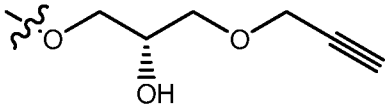
 ;  or  .

75. The compound of any one of claims 1 to 6, wherein Q is  ;  ;  ;

 ;  ;  ;  ,

 ;  ;

 ;  ;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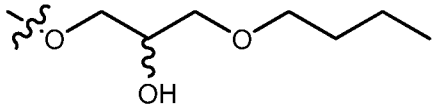
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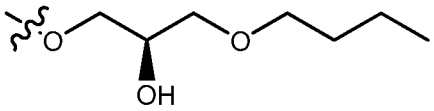
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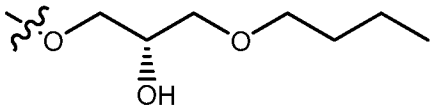
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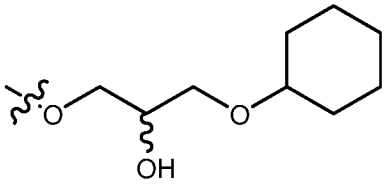
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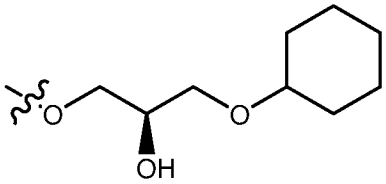
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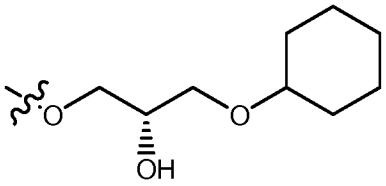
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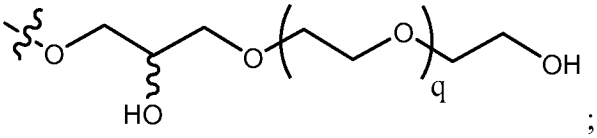
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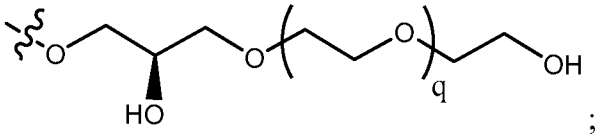
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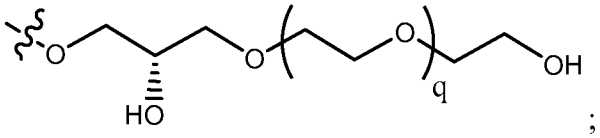
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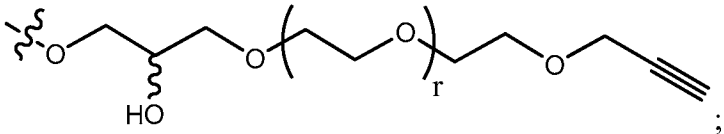
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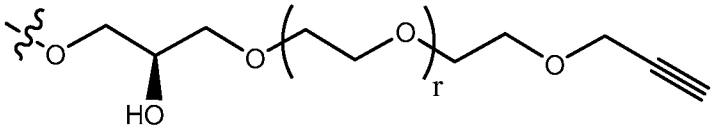
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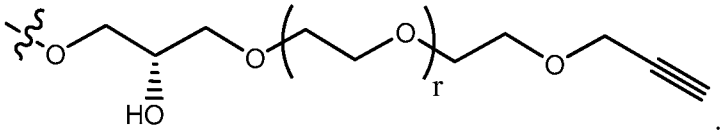
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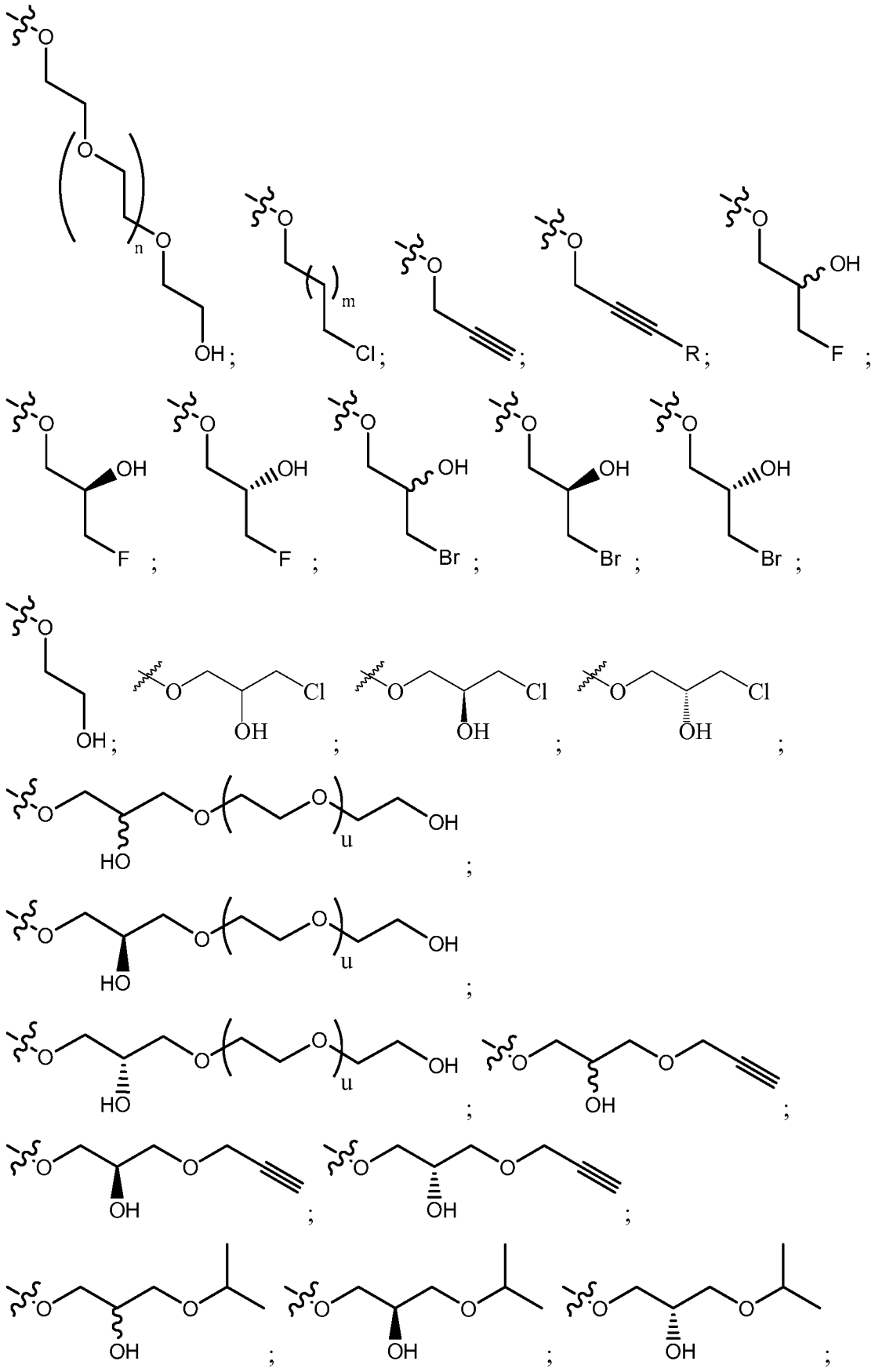
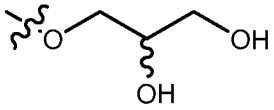
76. The compound of any one of claims 1 to 6, wherein T is

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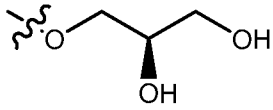
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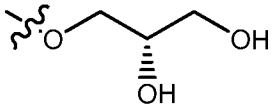
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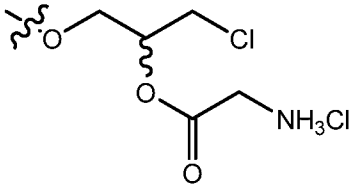
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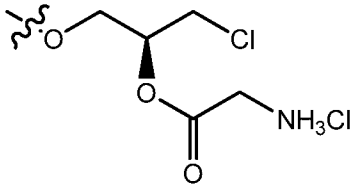
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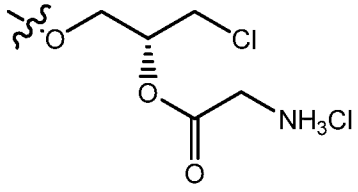
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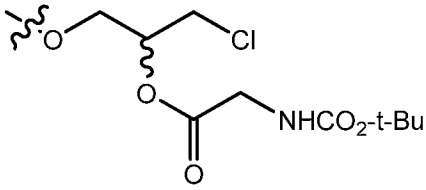
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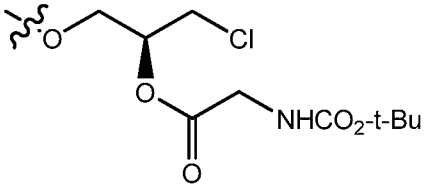
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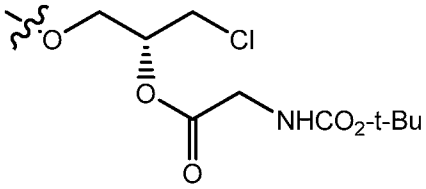
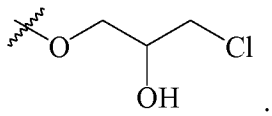

; and

n, m and q are each independently 0, 1, 2, 3, 4, 5, 6, 7 or 8.

77. The compound of any one of claims 1 to 6, wherein T is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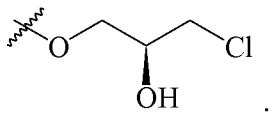
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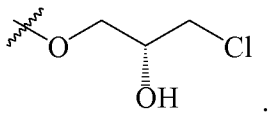
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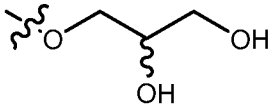
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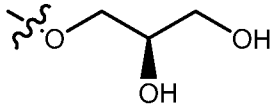
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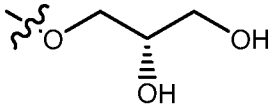
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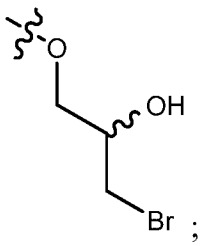
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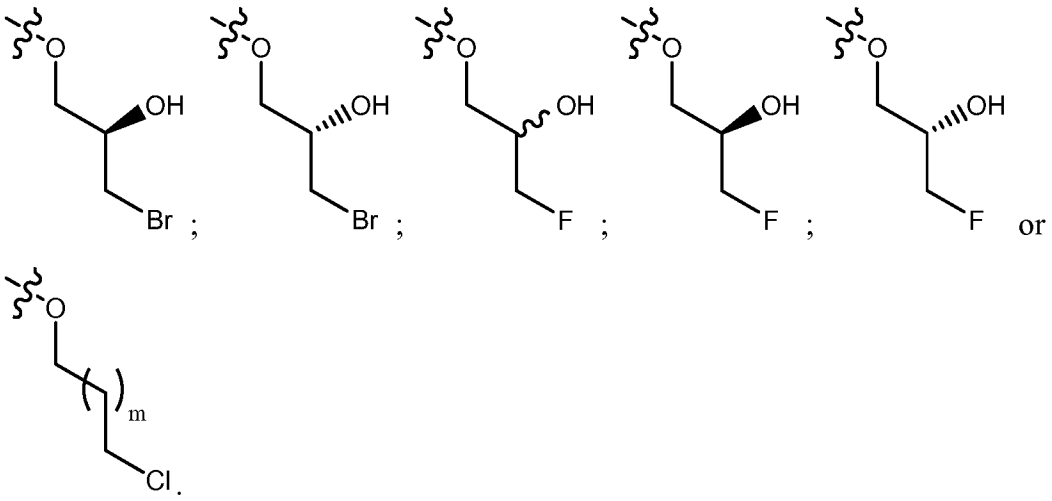
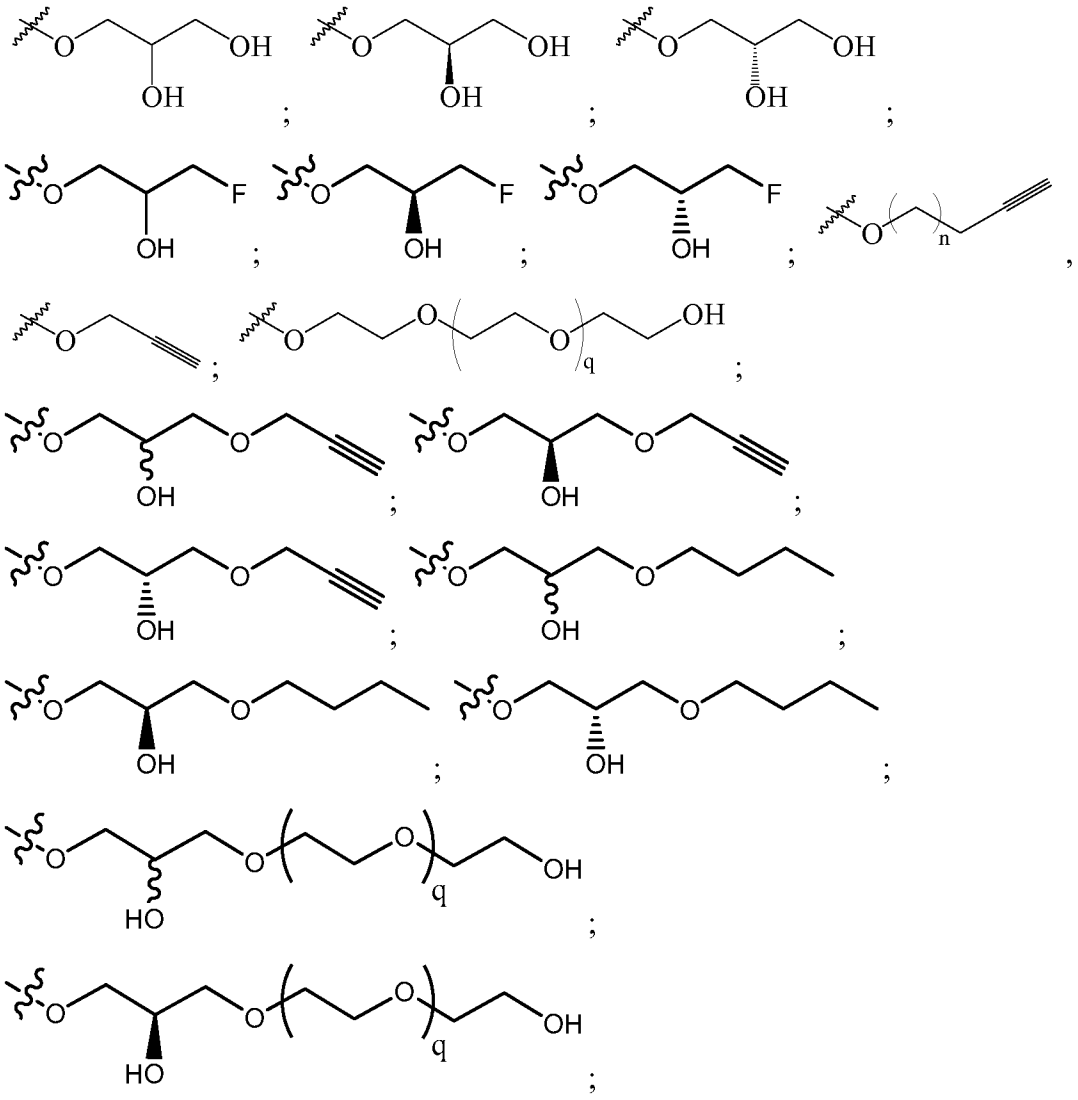
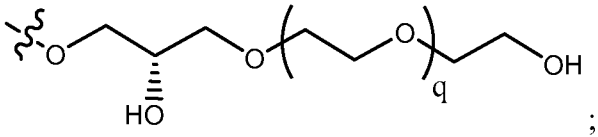


78. The compound of any one of claims 1 to 6, wherein Q is

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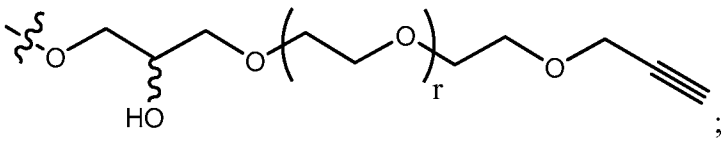
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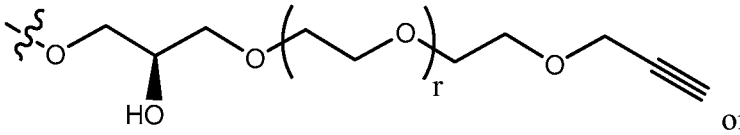
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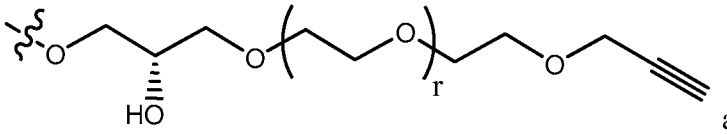
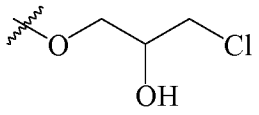

and T is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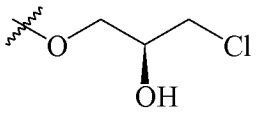
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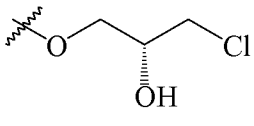
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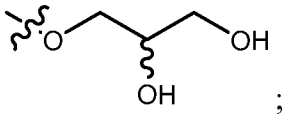
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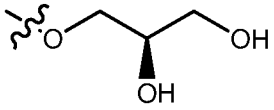
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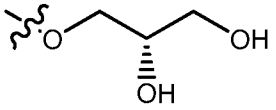
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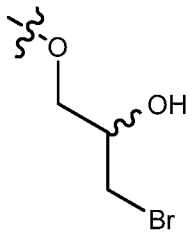
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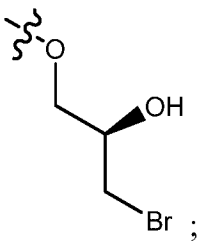
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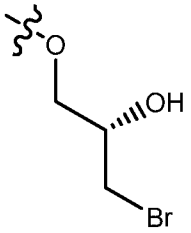
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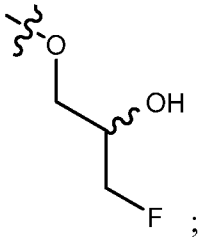
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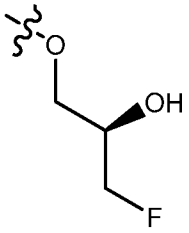
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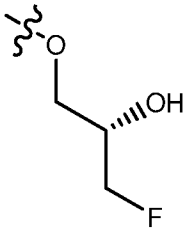
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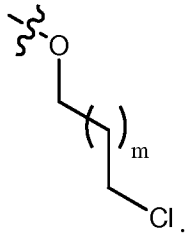
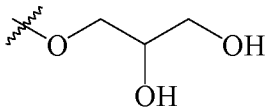

.

79. The compound of any one of claims 1 to 6, wherein Q is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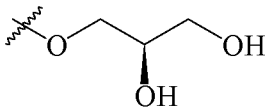
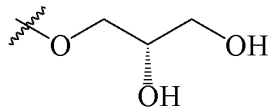
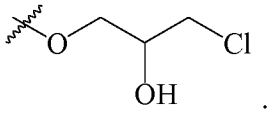

or


and T is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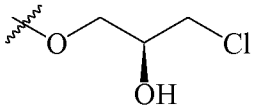
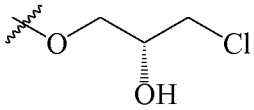
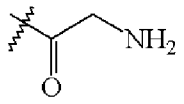
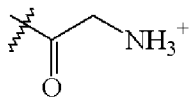

or


.

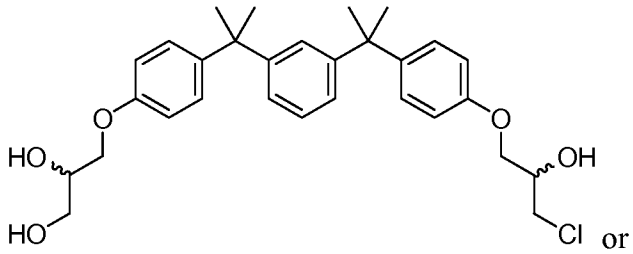
80. The compound of any one of claims 1 to 4, wherein each remaining Z^1, Z^2 and Z^3 is independently selected from: CCH_3; CH; CF, CCl, and CBr.

81. The compound of any one of claims 1 to 4, wherein each remaining Z^1, Z^2 and Z^3 is CH.

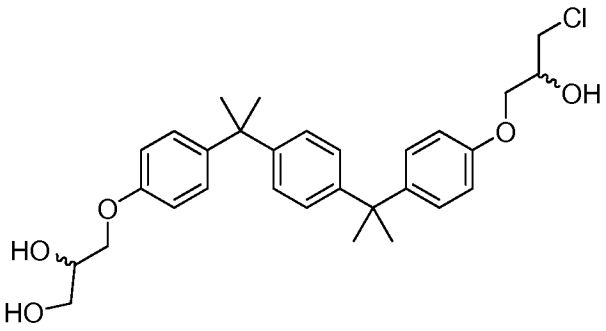
82. The compound of any one of claims 1 to 76, wherein one or more of the OH groups of the compound is substituted to replace the H with a moiety from TABLE 1.

83. The compound of claim 77, wherein the moiety from TABLE 1 is  or  .

84. A compound having one of the following structures:



or



.

85. Use of the compound of any one of claims 1 to 84, for modulating androgen receptor (AR) activity.

86. The use of claim 85, wherein modulating androgen receptor (AR) activity is in a mammalian cell.

87. The use of any one of claims 85 or 86, 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.

88. The use of claim 87, wherein the indication is prostate cancer.

89. The use of claim 88, wherein the prostate cancer is castration resistant prostate cancer.

90. The use of claim 89, wherein the prostate cancer is androgen-dependent prostate cancer.

91. The use of claim 87, wherein the spinal and bulbar muscular atrophy is Kennedy's disease.

92. A method of modulating androgen receptor (AR) activity, the method comprising administering a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 84 to a subject in need thereof.

93. The method of claim 92, 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.

94. The method of claim 93, wherein the prostate cancer is castration resistant prostate cancer.

95. The method of claim 93, wherein the prostate cancer is androgen-dependent prostate cancer.

96. The method of claim 93, wherein the spinal and bulbar muscular atrophy is Kennedy's disease.

97. A pharmaceutical composition comprising a compound of any one of claims 1 to 84 and a pharmaceutically acceptable carrier.

98. A pharmaceutical composition comprising a compound of any one of claims 1 to 84, an additional therapeutic agent and a pharmaceutically acceptable carrier.

99. The pharmaceutical composition of claim 98, 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.

100. The pharmaceutical composition of claim 98, wherein the additional therapeutic agent is MDV3100 , 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.

101. Use of the pharmaceutical composition of any one of claims 97 to 100 for modulating androgen receptor (AR) activity.

102. The use of claim 101, wherein modulating androgen receptor (AR) activity is in a mammalian cell.

103. The use of any one of claims 101 or 102, 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.

104. The use of claim 103, wherein the indication is prostate cancer.

105. The use of claim 104, wherein the prostate cancer is castration resistant prostate cancer.

106. The use of claim 104, wherein the prostate cancer is androgen-dependent prostate cancer.

107. The use of claim 103, wherein the spinal and bulbar muscular atrophy is Kennedy's disease.

108. A method of modulating androgen receptor (AR) activity, the method comprising administering the pharmaceutical composition of any one of claims 97 to 100 to a subject in need thereof.

109. The method of claim 108 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.

110. The method of claim 109, wherein the spinal and bulbar muscular atrophy is Kennedy's disease.

111. The use of claim 105, wherein the indication is prostate cancer.

112. The use of claim 111, wherein the prostate cancer is castration resistant prostate cancer.

113. The use of claim 111, wherein the prostate cancer is androgen-dependent prostate cancer.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/33957

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 31/14; A61K 31/075; C07C 43/295 (2012.01)
USPC - 514/721; 568/630
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)
IPC(8): A01N 31/14; A61K 31/075; C07C 43/295 (2012.01)
USPC: 514/721; 568/630

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/224.5, 325, 185 (text search0 Find search terms below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB,USPT,USOC,EPAB,JPAB), Google Scholar
anti-androgen, antiandrogen, androgen receptor, modulat$, antagonist$, bisphenol$, ether, tri-phenyl or triphenyl

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2010/000066 A1 (SADAR et al.) 07 January 2010 (07.01.2010) - especially pg 4, para 4 - pg 5, para 2; pg 5, para 3 - pg 6, para 1	1-8 and 84
Y	SATOH et al. 'Study on anti-androgenic effects of bisphenol a diglycidyl ether(BADGE), bisphenol F diglycidyl ether (BFDGE) and their derivatives using cells stably transfected with human androgen receptor, AR-EcoScreen', Food and Chemical Toxicology, 2004, Vol.42 pages 983-993. - especially pg 984, Fig.1; pg 987, col 1, para 3 - pg 991, col 2, para 1	1-8 and 84
A	US 4,904,760 A (GAKU et al.) 27 February 1990 (27.02.1990) - especially col 2, ln 10 - col 10, ln 39	1-8 and 84

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
01 July 2012 (01.07.2012)	18 JUL 2012

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/33957

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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

3. ☒ Claims Nos.: 9-83 and 85-113
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 claims Nos.:

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

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.