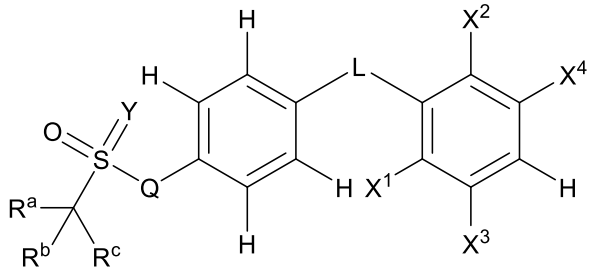
COVID-19 associated nephropathy and other viral nephropathies (Shetty, A. et al. *J. Am. Soc. Nephrol.* (2021) 32, 33-40; Chang, J. H. et al. *Am. J. Kidney Dis.* (2019) 73, 134-139). Moreover, decreased renal allograft survival has been observed after deceased-donor kidney transplantations from APOL1 high-risk genotype donors (Freedman, B. I. et al. *Transplantation.* (2016) 100, 194-202). In addition, having two APOL1 risk alleles increases risk for preeclampsia (Reidy, K. J. et al. *Am. J. Hum. Genet.* (2018) 103, 367-376) and sepsis (Chaudhary, N. S. et al. *Clin. J. Am. Soc. Nephrol.* (2019) 14, 1733-1740). There are no approved therapies for APOL1-associated nephropathy, and patients are treated based on the standard of care for their underlying form of chronic kidney disease. This presents a clear unmet need for therapies targeted to people with the APOL1 high-risk genotype.

[0004] Numerous studies have shown that APOL1 risk variants are toxic when overexpressed in human cells (Wan, G. et al. *J. Biol. Chem.* (2008) 283, 21540-21549; Lan, X. et al. *Am. J. Physiol. Renal Physiol.* (2014) 307, F326-F336; Olabisi, O. A. et al. *Proc. Natl. Acad. Sci. USA.* (2016) 113, 830-837; Ma, L. et al. *J. Am. Soc. Nephrol.* (2017) 28, 1093-1105; Lannon, H. et al. *Kidney Int.* (2019) 96, 1303-1307). Recent findings suggest that this toxicity is associated with APOL1 pore function (Giovinazzo, J. A. et al. *eLife.* (2020) 9, e51185). Thus, there is a need to develop compounds suitable for inhibiting APOL1 activity and methods for inhibiting the activity of APOL1 using such compounds.

BRIEF SUMMARY

[0004a] In a first aspect of the present disclosure, there is provided a compound of formula (A'):



(A'),

or a stereoisomer or a tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

Q is absent or is -N-(C_{1-6}alkyl);

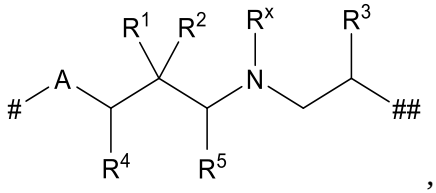
Y is O or -N-(C_{1-6}alkyl),

provided that, when Q is -N(C_{1-6}alkyl), then Y is O;

R^a, R^b, and R^c are each independently H or C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^a, R^b, or R^c is independently optionally substituted with one or more -OH, C_{1-6}alkoxy, or -$S(O)_2$-C_{1-6}alkyl,

or any two of R^a, R^b, and R^c are taken, together with the atoms to which they are attached, to form a C_{3-6}cycloalkyl or a 3-6 membered heterocyclyl, and the other of R^a, R^b, and R^c is H or C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^a, R^b, or R^c is independently optionally substituted with one or more -OH, C_{1-6}alkoxy, or -$S(O)_2$-C_{1-6}alkyl;

L is selected from the group consisting of:

(i) 

, wherein

A is O, NH, N(C_{1-6}alkyl), CH_2, or CH(C_{1-6}alkyl);

R^x is H,

or R^x is taken together with one of R^1 and R^2, and the atoms to which they are attached, to form a 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl is substituted with *n* independently selected R^g substituents, wherein *n* is an integer from 0-6, and R^g is -OH, halo, C_{1-6}alkyl, or C_{1-6}alkoxy;

R^1 and R^2 are independently H, halo, or -OH,

or one of R^1 and R^2 is taken together with R^x, and the atoms to which they are attached, to form a 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl is substituted with *n* independently selected R^g substituents, wherein *n* is an integer from 0-6, and R^g is -OH, halo, C_{1-6}alkyl, or C_{1-6}alkoxy, and the other of R^1 and R^2 is H, halo, or -OH;

R^3 is H, -OH, halo, or C_{1-6}alkoxy; and

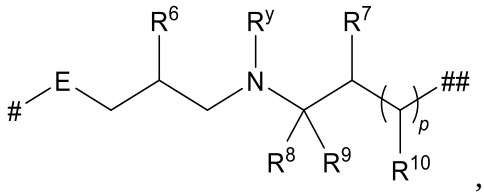
R^4 and R^5 are independently H,

or R^4 and R^5 are taken, together with the atoms to which they are attached, to form a C_{3-8}cycloalkyl,

provided that either:

(1) R^x is taken together with one of R^1 and R^2, and the atoms to which they are attached, to form a 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl is substituted with *n* independently selected R^g substituents, wherein *n* is an integer from 0-6, and R^g is -OH, halo, C_{1-6}alkyl, or C_{1-6}alkoxy, or

(2) R^4 and R^5 are taken, together with the atoms to which they are attached, to form a C_{3-8}cycloalkyl,

(ii) 

, wherein

E is O, NH, N(C_{1-6}alkyl), CH_2, or CH(C_{1-6}alkyl);

p is 0 or 1,

provided that, when *p* is 1, then E is O;

R^6 is H or -OH;

R^y is H,

or R^y is taken together with R^7, and the atoms to which they are attached, to form a 3-8 membered heterocyclyl,

or R^y is taken together with one of R^8 and R^9, and the atoms to which they are attached, to form a 3-8 membered heterocyclyl;

R^7 is H,

or R^7 is taken together with R^y, and the atoms to which they are attached, to form a 3-8 membered heterocyclyl;

R^8 and R^9 are independently H or C_{1-6}alkyl,

or one of R^8 and R^9 is taken together with R^y, and the atoms to which they are attached, to form a 3-8 membered heterocyclyl, and the other of R^8 and R^9 is H or C_{1-6}alkyl,

or one of R^8 and R^9 is taken together with R^{10}, and the atoms to which they are attached, to form a C_{3-8}cycloalkyl, and the other of R^8 and R^9 is H or C_{1-6}alkyl; and

R^{10} is H,

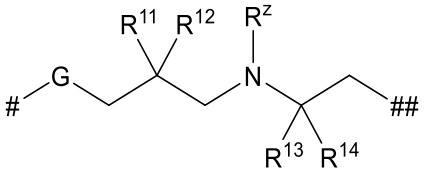
or R^{10} is taken together with one of R^8 and R^9, and the atoms to which they are attached, to form a C_{3-8}cycloalkyl,

provided that:

(1) R^y is taken together with R^7, and the atoms to which they are attached, to form a 3-8 membered heterocyclyl, or

(2) R^y is taken together with one of R^8 and R^9, and the atoms to which they are attached, to form a 3-8 membered heterocyclyl, or

(3) one of R^8 and R^9 is taken together with R^{10} and the atoms to which they are attached, to form a C_{3-8}cycloalkyl, and

(iii) 

, wherein

G is O, NH, N(C_{1-6}alkyl), CH_2, or CH(C_{1-6}alkyl);

R^z is H or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more C_{3-8}cycloalkyl;

R^{11} and R^{12} are independently H, -OH, halo, or C_{1-6}alkyl; and

R^{13} and R^{14} are independently H, C_{1-6}alkyl, or C_{3-8}cycloalkyl,

or R^{13} and R^{14} are taken, together with the atoms to which they are attached, to form a 3-8 membered heterocyclyl,

wherein, for each of (i)-(iii), # denotes the point of attachment to the phenyl ring bearing moiety Q, and ## denotes the point of attachment to the phenyl ring bearing moieties X^1-X^4; and

X^1, X^2, X^3, and X^4 are, independently of each other, H, halo, -CN, C_{1-6}alkyl, C_{1-6}alkoxy, or SF_5, wherein the C_{1-6}alkyl or C_{1-6}alkoxy is optionally substituted with one or more halo,

provided that at least one of X^1, X^2, X^3, and X^4 is halo, -CN, C_{1-6}alkyl, C_{1-6}alkoxy, or SF_5, wherein the C_{1-6}alkyl or C_{1-6}alkoxy is optionally substituted with one or more halo.

[0004b] In another aspect of the present disclosure, there is provided a pharmaceutical composition, comprising (i) a compound as disclosed herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) one or more pharmaceutically acceptable excipients.

[0004c] In yet another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for modulating APOL1 in a cell.

[0004d] In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for inhibiting APOL1 in a cell.

[0004e] In another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating an APOL1-mediated disease, disorder, or condition in an individual in need thereof.

[0004f] In yet another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for delaying the development of an APOL1-mediated disease, disorder, or condition.

[0004g] In a further aspect of the present disclosure, there is provided a kit, comprising (i) a compound as disclosed herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition as disclosed herein, and (ii) instructions for use in treating an APOL1-mediated disease, disorder, or condition in an individual in need thereof.

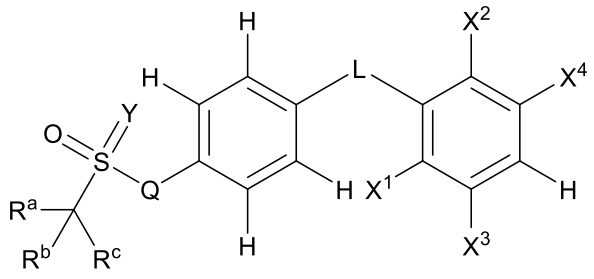
[0004h] In another aspect of the present disclosure, there is provided a compound as disclosed herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition as disclosed herein, for use in therapy.

[0005] This disclosure describes compounds and compositions that may be useful for the treatment of APOL1-mediated diseases, including a variety of chronic kidney diseases such as FSGS, hypertension-attributed kidney disease, HIVAN, sickle cell nephropathy, lupus nephritis, diabetic kidney disease, viral nephropathy, COVID-19 associated nephropathy, and APOL1-associated nephropathy. The compounds and compositions may also find use in treating other APOL1-mediated disorders such as preeclampsia and sepsis. Additionally, for individuals

with the APOL1 high-risk genotype, the disclosed compounds and compositions could have utility in preventing the onset of non-diabetic renal disease and/or delaying the progression of any form of chronic kidney disease. The disclosed chemical matter could also have utility in preventing and/or delaying progressive renal allograft loss in patients who have received a kidney transplant from a high-risk APOL1 genotype donor.

[0006] In one example, provided herein is a compound of formula (A'):

[0007] In one example, provided herein is a compound of formula (A):



(A),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

Q is absent or is -N-(C_{1-6}alkyl);

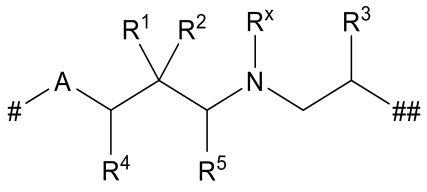
Y is O or -N-(C_{1-6}alkyl),

provided that, when Q is -N(C_{1-6}alkyl), then Y is O;

R^a, R^b, and R^c are each independently H or C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^a, R^b, or R^c is independently optionally substituted with one or more -OH, C_{1-6}alkoxy, or -$S(O)_2$-C_{1-6}alkyl,

or any two of R^a, R^b, and R^c are taken, together with the atoms to which they are attached, to form a C_{3-6}cycloalkyl or a 3-6 membered heterocyclyl, and the other of R^a, R^b, and R^c is H or C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^a, R^b, or R^c is independently optionally substituted with one or more -OH, C_{1-6}alkoxy, or -$S(O)_2$-C_{1-6}alkyl;

L is selected from the group consisting of:

(i)  , wherein

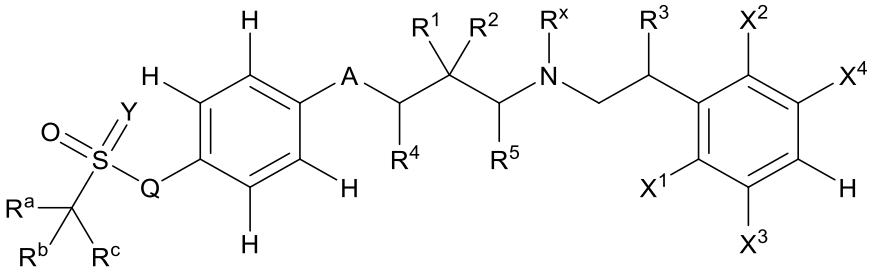
A is O, NH, N(C_{1-6}alkyl), CH_2, or CH(C_{1-6}alkyl);

R^x is H,

provided that at least one of X^1, X^2, X^3, and X^4 is halo, -CN, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl or C_{1-6}alkoxy is optionally substituted with one or more halo.

[0008] Any examples provided herein of a compound of formula (A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or example thereof, are also examples of a compound of formula (A'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or example thereof.

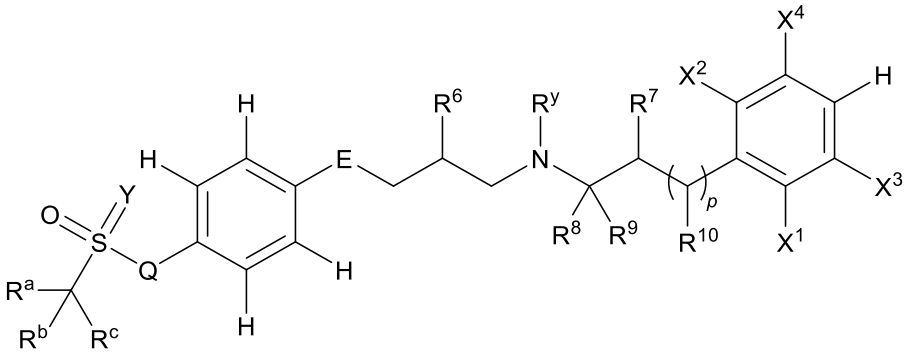
[0009] In one example, provided herein is a compound of formula (I):



(I),

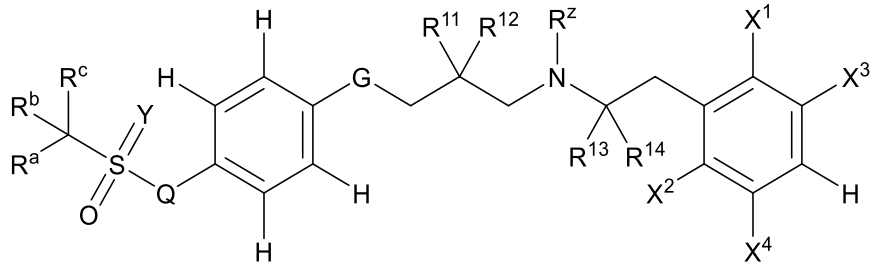
or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^1, X^2, X^3, X^4, R^1, R^2, R^3, R^4, R^5, R^a, R^b, R^c, R^x, A, Q, and Y are as defined for a compound of formula (A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or example thereof. In another variation, X^1, X^2, X^3, X^4, R^1, R^2, R^3, R^4, R^5, R^a, R^b, R^c, R^x, A, Q, and Y of formula (I) are as defined for a compound of formula (A'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or example thereof.

[0010] In one example, provided herein is a compound of formula (II):



(II),

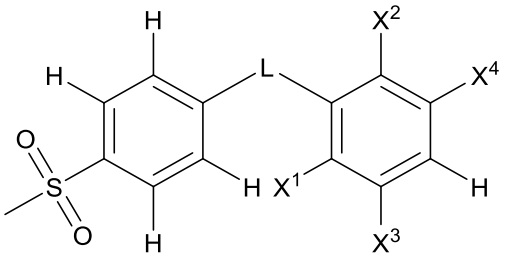
[0011] or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^1, X^2, X^3, X^4, R^6, R^7, R^8, R^9, R^{10}, R^a, R^b, R^c, R^y, *p*, E, Q, and Y are as defined for a compound of formula (A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or example thereof. In another variation, X^1, X^2, X^3, X^4, R^6, R^7, R^8, R^9, R^{10}, R^a, R^b, R^c, R^y, *p*, E, Q, and Y of formula (II) are as defined for a compound of formula (A'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or example thereof.In one example, provided herein is a compound of formula (III):



(III),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^1, X^2, X^3, X^4, R^{11}, R^{12}, R^{13}, R^{14}, R^a, R^b, R^c, R^z, G, Q, and Y are as defined for a compound of formula (A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or example thereof. In another variation, X^1, X^2, X^3, X^4, R^{11}, R^{12}, R^{13}, R^{14}, R^a, R^b, R^c, R^z, G, Q, and Y of formula (III) are as defined for a compound of formula (A'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or example thereof.

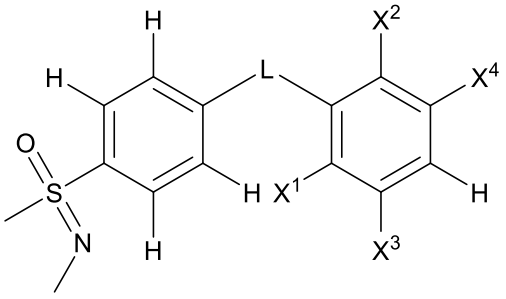
[0012] In one example, provided herein is a compound of formula (B-2):



(B-2),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^1, X^2, X^3, X^4, and L are as defined for a compound of formula (A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or example thereof. In another variation, X^1, X^2, X^3, X^4, and L of formula (B-2) are as defined for a compound of formula (A'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or example thereof.

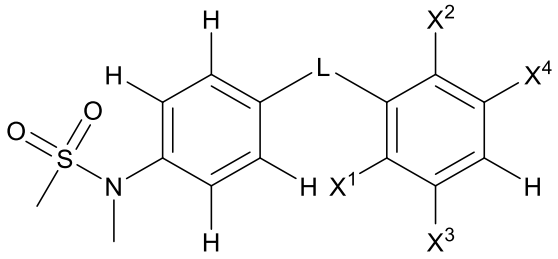
[0013] In one example, provided herein is a compound of formula (B-5):



(B-5),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^1, X^2, X^3, X^4, and L are as defined for a compound of formula (A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or example thereof. In another variation, X^1, X^2, X^3, X^4, and L of formula (B-5) are as defined for a compound of formula (A'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or example thereof.

[0014] In one example, provided herein is a compound of formula (C-1):



(C-1),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^1, X^2, X^3, X^4, and L are as defined for a compound of formula (A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or example thereof. In another variation, X^1, X^2, X^3, X^4, and L of formula (C-1) are as defined for a compound of formula (A'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or example thereof.

[0015] In one example, provided herein is a pharmaceutical composition, comprising (i) a compound of formula (A), or any example or variation thereof, such as a compound of formula (I), (II), (III), (B-2), (B-5), or (C-1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) one or more pharmaceutically acceptable excipients. In another variation, provided herein is a pharmaceutical composition, comprising (i) a compound of formula (A'), or any example or variation thereof, such as a compound of formula (I), (II), (III), (B-2), (B-5), or (C-1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) one or more pharmaceutically acceptable excipients.

[0016] In one example, provided herein is a method of modulating APOL1 in a cell, comprising exposing the cell to a composition comprising an effective amount of a compound of formula (A), or any example or variation thereof, such as a compound of formula (I), (II), (III), (B-2), (B-5), or (C-1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition comprising (i) a compound of formula (A), or any example or variation thereof, such as a compound of formula (I), (II), (III), (B-2), (B-5), or (C-1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) one or more pharmaceutically acceptable excipients. In another variation, provided herein is a method of modulating APOL1 in a cell, comprising exposing the cell to a composition comprising an effective amount of a compound of formula (A'), or any example or variation thereof, such as a compound of formula (I), (II), (III), (B-2), (B-5), or (C-1), or a stereoisomer or tautomer thereof, or a

pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition comprising (i) a compound of formula (A'), or any example or variation thereof, such as a compound of formula (I), (II), (III), (B-2), (B-5), or (C-1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) one or more pharmaceutically acceptable excipients.

[0017] In one example, provided herein is a method of inhibiting APOL1 in a cell, comprising exposing the cell to a composition comprising an effective amount of a compound of formula (A), or any example or variation thereof, such as a compound of formula (I), (II), (III), (B-2), (B-5), or (C-1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition comprising (i) a compound of formula (A), or any example or variation thereof, such as a compound of formula (I), (II), (III), (B-2), (B-5), or (C-1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) one or more pharmaceutically acceptable excipients. In another variation, provided herein is a method of inhibiting APOL1 in a cell, comprising exposing the cell to a composition comprising an effective amount of a compound of formula (A'), or any example or variation thereof, such as a compound of formula (I), (II), (III), (B-2), (B-5), or (C-1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition comprising (i) a compound of formula (A'), or any example or variation thereof, such as a compound of formula (I), (II), (III), (B-2), (B-5), or (C-1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) one or more pharmaceutically acceptable excipients.

[0018] In one example, provided herein is a method of treating an APOL1-mediated disease, disorder, or condition in an individual in need thereof, comprising administering to the individual an effective amount of a compound of formula (A), or any example or variation thereof, such as a compound of formula (I), (II), (III), (B-2), (B-5), or (C-1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition comprising (i) a compound of formula (A), or any example or variation thereof, such as a compound of formula (I), (II), (III), (B-2), (B-5), or (C-1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) one or more pharmaceutically acceptable excipients. In another variation, provided herein is a method of treating an APOL1-mediated disease, disorder, or condition in an

individual in need thereof, comprising administering to the individual an effective amount of a compound of formula (A'), or any example or variation thereof, such as a compound of formula (I), (II), (III), (B-2), (B-5), or (C-1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition comprising (i) a compound of formula (A'), or any example or variation thereof, such as a compound of formula (I), (II), (III), (B-2), (B-5), or (C-1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) one or more pharmaceutically acceptable excipients.

[0019] In one example, provided herein is a kit, comprising (i) a compound of formula (A), or any example or variation thereof, such as a compound of formula (I), (II), (III), (B-2), (B-5), or (C-1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) instructions for use in treating an APOL1-mediated disease, disorder, or condition in an individual in need thereof. In another variation, provided herein is a kit, comprising (i) a compound of formula (A'), or any example or variation thereof, such as a compound of formula (I), (II), (III), (B-2), (B-5), or (C-1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) instructions for use in treating an APOL1-mediated disease, disorder, or condition in an individual in need thereof.

[0020] In some example, provided herein are methods of preparing a compound of formula (A) or (A'), or any example or variation thereof, such as a compound of formula (I), (II), (III), (B-2), (B-5), or (C-1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

DETAILED DESCRIPTION OF THE INVENTION

[0021] Unless clearly indicated otherwise, the terms "a," "an," and the like, refer to one or more.

[0022] As used herein, "about" a parameter or value includes and describes that parameter or value per se. For example, "about X" includes and describes X per se.

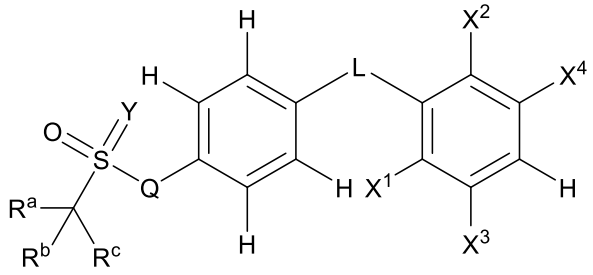
[0023] "Individual" refers to mammals and includes humans and non-human mammals. Examples of individuals include, but are not limited to, some primates and humans. In some embodiments, individual refers to a human.

[0024] As used herein, an "at risk" individual is an individual who is at risk of developing a disease or condition. An individual "at risk" may or may not have a detectable

CLAIMS

What is claimed is:

1. A compound of formula (A'):



(A'),

or a stereoisomer or a tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

Q is absent or is -N-(C_{1-6}alkyl);

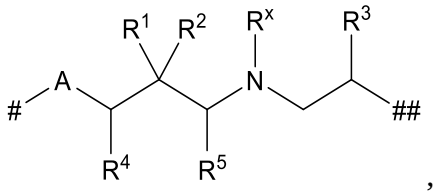
Y is O or -N-(C_{1-6}alkyl),

provided that, when Q is -N(C_{1-6}alkyl), then Y is O;

R^a, R^b, and R^c are each independently H or C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^a, R^b, or R^c is independently optionally substituted with one or more -OH, C_{1-6}alkoxy, or -$S(O)_2$-C_{1-6}alkyl,

or any two of R^a, R^b, and R^c are taken, together with the atoms to which they are attached, to form a C_{3-6}cycloalkyl or a 3-6 membered heterocyclyl, and the other of R^a, R^b, and R^c is H or C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^a, R^b, or R^c is independently optionally substituted with one or more -OH, C_{1-6}alkoxy, or -$S(O)_2$-C_{1-6}alkyl;

L is selected from the group consisting of:

(i) 

, wherein

A is O, NH, N(C_{1-6}alkyl), CH_2, or CH(C_{1-6}alkyl);

R^x is H,

or R^x is taken together with one of R^1 and R^2, and the atoms to which they are attached, to form a 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl is substituted with *n* independently selected R^g substituents, wherein *n* is an integer from 0-6, and R^g is -OH, halo, C_{1-6}alkyl, or C_{1-6}alkoxy;

R^1 and R^2 are independently H, halo, or -OH,

or one of R^1 and R^2 is taken together with R^x, and the atoms to which they are attached, to form a 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl is substituted with *n* independently selected R^g substituents, wherein *n* is an integer from 0-6, and R^g is -OH, halo, C_{1-6}alkyl, or C_{1-6}alkoxy, and the other of R^1 and R^2 is H, halo, or -OH;

R^3 is H, -OH, halo, or C_{1-6}alkoxy; and

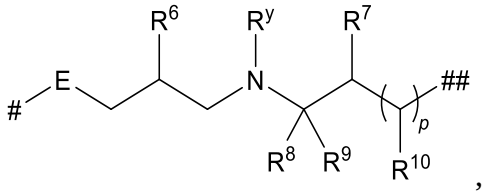
R^4 and R^5 are independently H,

or R^4 and R^5 are taken, together with the atoms to which they are attached, to form a C_{3-8}cycloalkyl,

provided that either:

(1) R^x is taken together with one of R^1 and R^2, and the atoms to which they are attached, to form a 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl is substituted with *n* independently selected R^g substituents, wherein *n* is an integer from 0-6, and R^g is -OH, halo, C_{1-6}alkyl, or C_{1-6}alkoxy, or

(2) R^4 and R^5 are taken, together with the atoms to which they are attached, to form a C_{3-8}cycloalkyl,

(ii) 

, wherein

E is O, NH, N(C_{1-6}alkyl), CH_2, or CH(C_{1-6}alkyl);

p is 0 or 1,

provided that, when *p* is 1, then E is O;

R^6 is H or -OH;

R^y is H,

or R^y is taken together with R^7, and the atoms to which they are attached, to form a 3-8 membered heterocyclyl,

or R^y is taken together with one of R^8 and R^9, and the atoms to which they are attached, to form a 3-8 membered heterocyclyl;

R^7 is H,

or R^7 is taken together with R^y, and the atoms to which they are attached, to form a 3-8 membered heterocyclyl;

R^8 and R^9 are independently H or C_{1-6}alkyl,

or one of R^8 and R^9 is taken together with R^y, and the atoms to which they are attached, to form a 3-8 membered heterocyclyl, and the other of R^8 and R^9 is H or C_{1-6}alkyl,

or one of R^8 and R^9 is taken together with R^{10}, and the atoms to which they are attached, to form a C_{3-8}cycloalkyl, and the other of R^8 and R^9 is H or C_{1-6}alkyl; and

R^{10} is H,

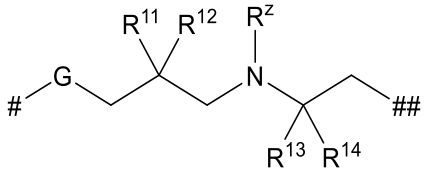
or R^{10} is taken together with one of R^8 and R^9, and the atoms to which they are attached, to form a C_{3-8}cycloalkyl,

provided that:

(1) R^y is taken together with R^7, and the atoms to which they are attached, to form a 3-8 membered heterocyclyl, or

(2) R^y is taken together with one of R^8 and R^9, and the atoms to which they are attached, to form a 3-8 membered heterocyclyl, or

(3) one of R^8 and R^9 is taken together with R^{10} and the atoms to which they are attached, to form a C_{3-8}cycloalkyl, and

(iii) 

, wherein

G is O, NH, N(C_{1-6}alkyl), CH_2, or CH(C_{1-6}alkyl);

R^z is H or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more C_{3-8}cycloalkyl;

R^{11} and R^{12} are independently H, -OH, halo, or C_{1-6}alkyl; and

R^{13} and R^{14} are independently H, C_{1-6}alkyl, or C_{3-8}cycloalkyl,

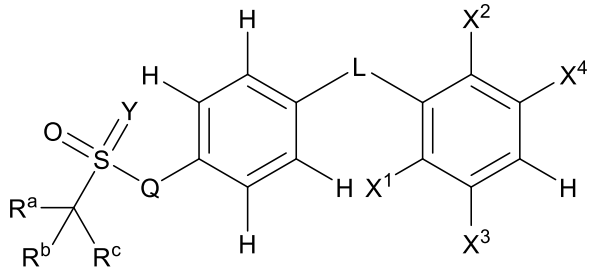
or R^{13} and R^{14} are taken, together with the atoms to which they are attached, to form a 3-8 membered heterocyclyl,

wherein, for each of (i)-(iii), # denotes the point of attachment to the phenyl ring bearing moiety Q, and ## denotes the point of attachment to the phenyl ring bearing moieties X^1-X^4; and

X^1, X^2, X^3, and X^4 are, independently of each other, H, halo, -CN, C_{1-6}alkyl, C_{1-6}alkoxy, or SF_5, wherein the C_{1-6}alkyl or C_{1-6}alkoxy is optionally substituted with one or more halo,

provided that at least one of X^1, X^2, X^3, and X^4 is halo, -CN, C_{1-6}alkyl, C_{1-6}alkoxy, or SF_5, wherein the C_{1-6}alkyl or C_{1-6}alkoxy is optionally substituted with one or more halo.

2. The compound of claim 1, wherein the compound is a compound of formula (A):

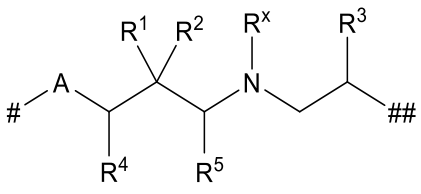


(A),

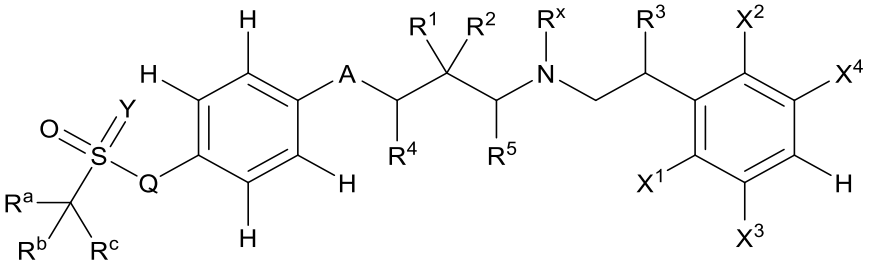
or a stereoisomer or a tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

X^1, X^2, X^3, and X^4 are, independently of each other, H, halo, -CN, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl or C_{1-6}alkoxy is optionally substituted with one or more halo,

provided that at least one of X^1, X^2, X^3, and X^4 is halo, -CN, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl or C_{1-6}alkoxy is optionally substituted with one or more halo.

3. The compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein L is 

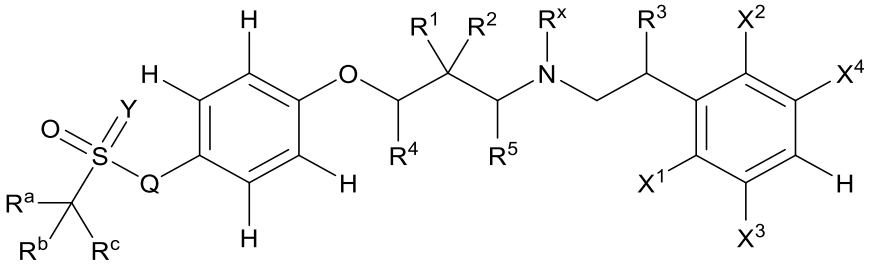
, such that the compound is of formula (I):



(I),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

4. The compound of claim 3, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein A is O, such that the compound is of formula (I-A):

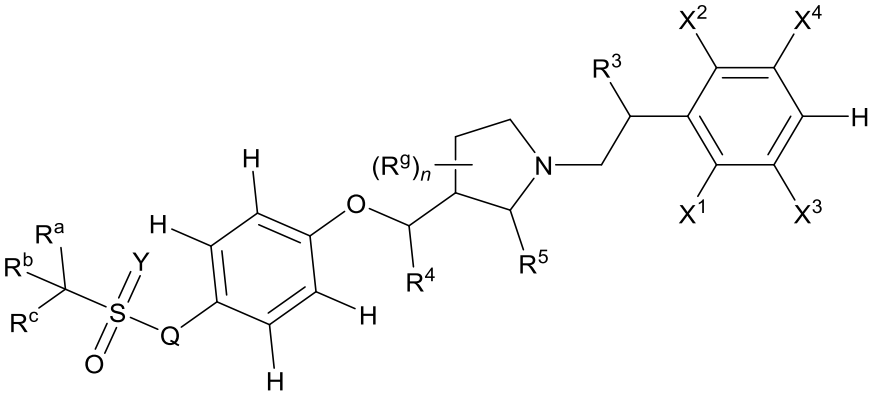


(I-A1),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

5. The compound of claim 4, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^x is taken together with one of R^1 and R^2, and the atoms to which they are attached, to form a 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl is substituted with *n* independently selected R^g substituents, wherein *n* is an integer from 0-6, and R^g is -OH, halo, C_{1-6}alkyl, or C_{1-6}alkoxy.

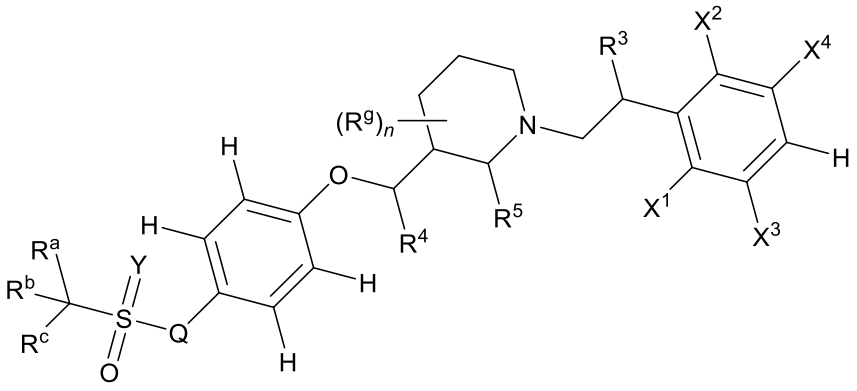
6. The compound of claim 5, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is of formula (I-B1):



(I-B1),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

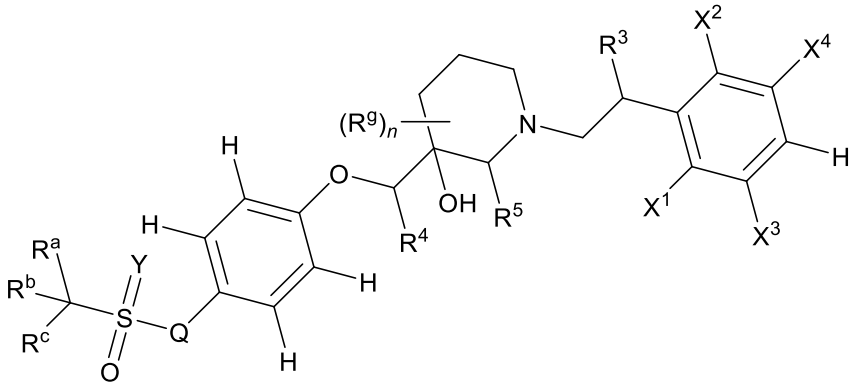
7. The compound of claim 5, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is of formula (I-C1):



(I-C1),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

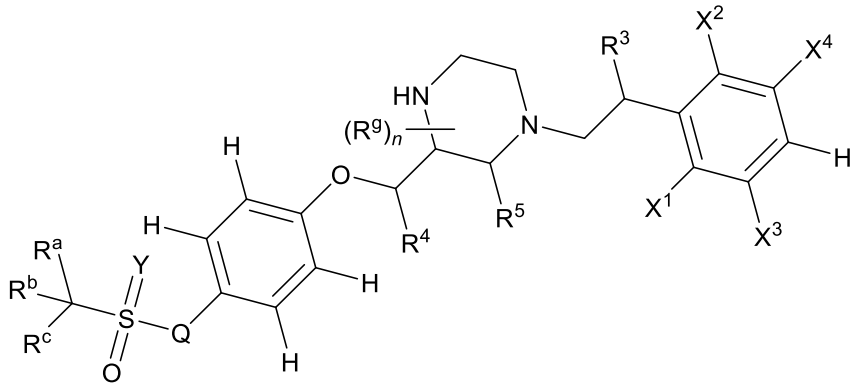
8. The compound of claim 5, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is of formula (I-D1):



(I-D1),

wherein or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

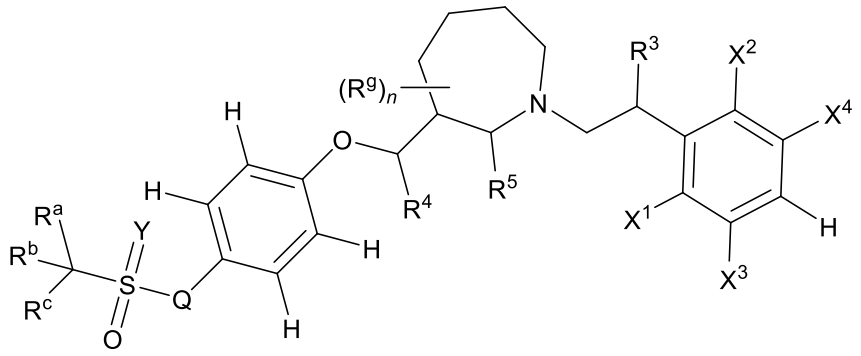
9. The compound of claim 5, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is of formula (I-E1):



(I-E1),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

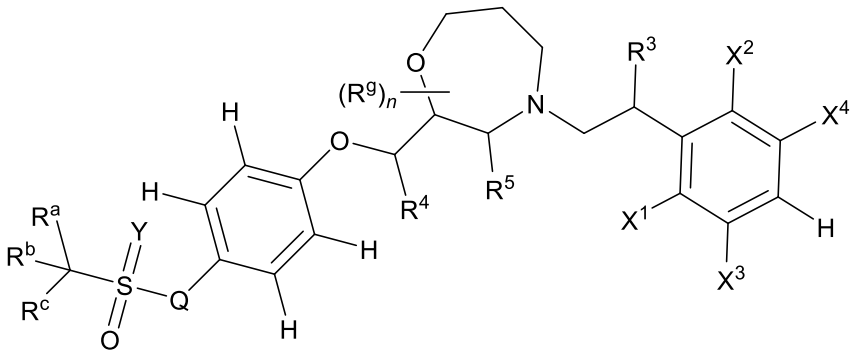
10. The compound of claim 5, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is of formula (I-F1):



(I-F1),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

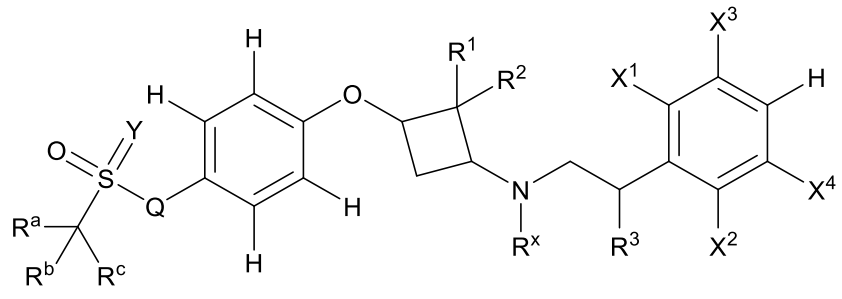
11. The compound of claim 5, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is of formula (I-G1):



(I-G1),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

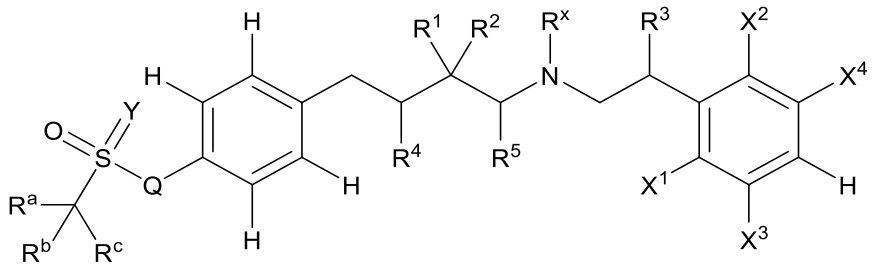
12. The compound of claim 4, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is of formula (I-H1):



(I-H1),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

13. The compound of claim 3, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein A is CH_2, such that the compound is of formula (I-A3):

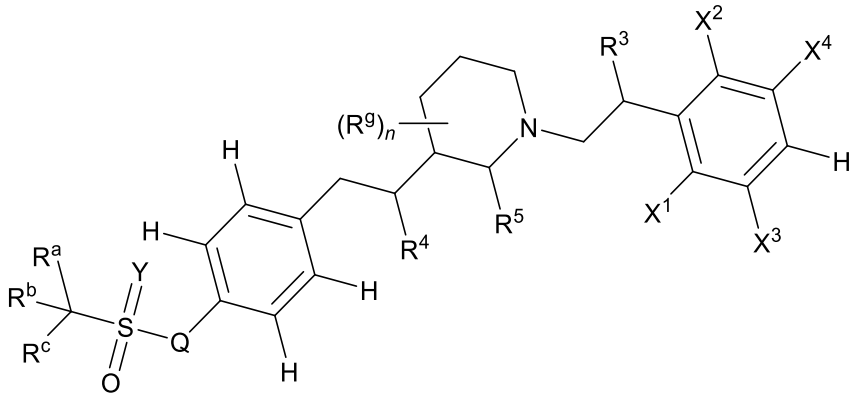


(I-A3),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

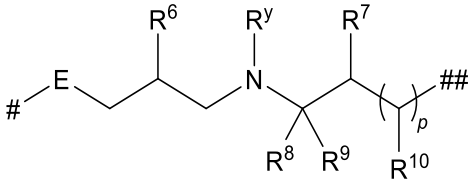
14. The compound of claim 13, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^x is taken together with one of R^1 and R^2, and the atoms to which they are attached, to form a 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl is substituted with *n* independently selected R^g substituents, wherein *n* is an integer from 0-6, and R^g is -OH, halo, $C_{1\text{-}6}$alkyl, or $C_{1\text{-}6}$alkoxy, and the other of R^1 and R^2 is H, halo, or -OH.

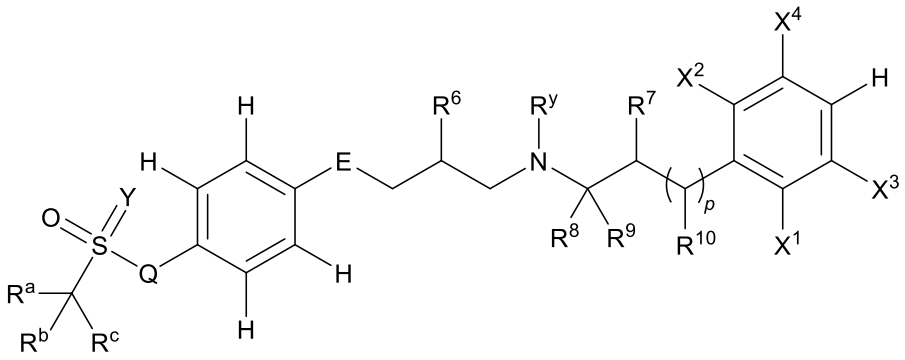
15. The compound of claim 14, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is of formula (I-C3):



(I-C3),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

16. The compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein L is , such that the compound is of formula (II):

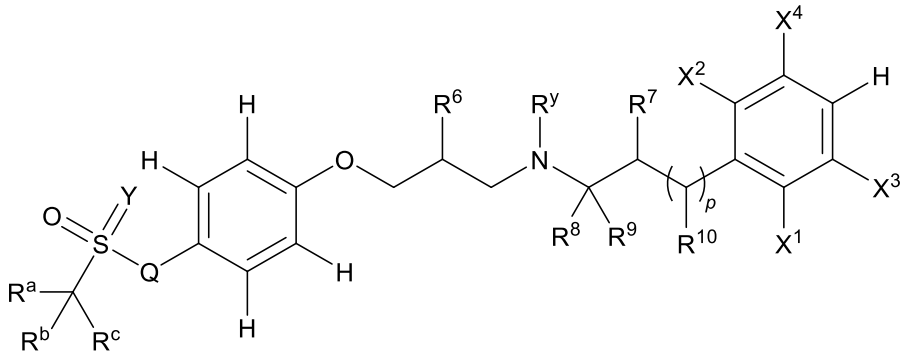


(II),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

17. The compound of claim 16, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein E is O, such that the compound is of formula (II-

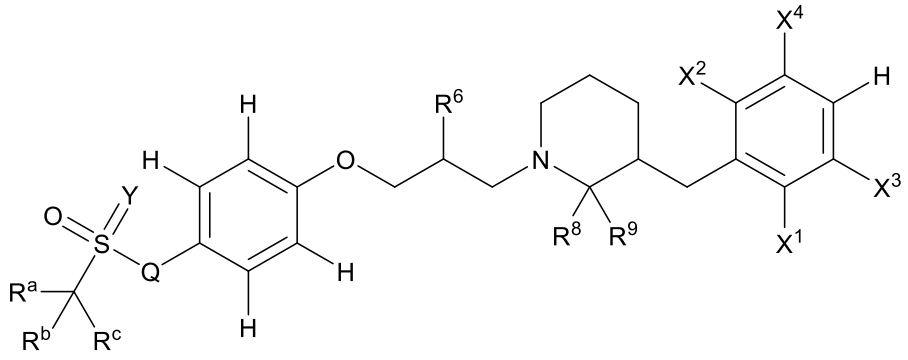
A1):



(II-A1),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

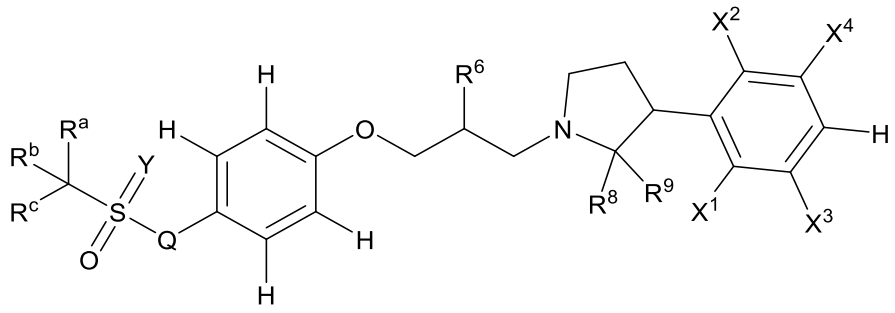
18. The compound of claim 17, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is of formula (II-B1):



(II-B1),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

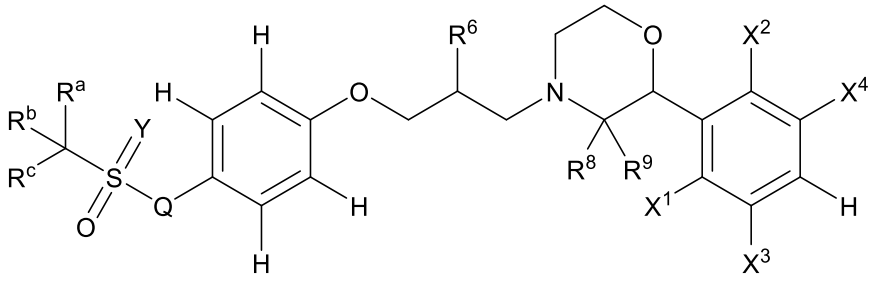
19. The compound of claim 17, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is of formula (II-C1):



(II-C1),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

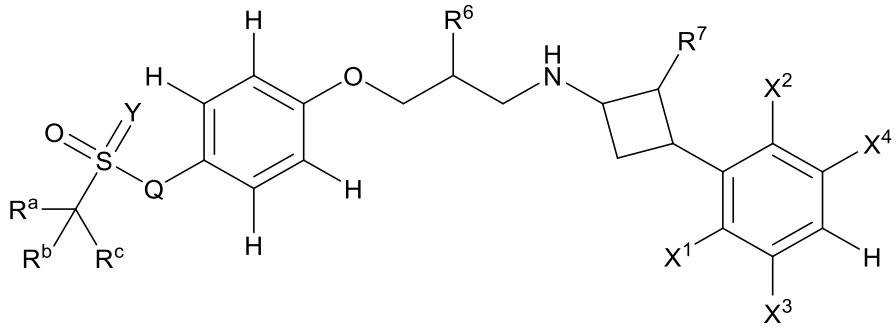
20. The compound of claim 17, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is of formula (II-D1):



(II-D1),

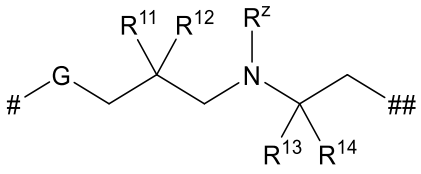
or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

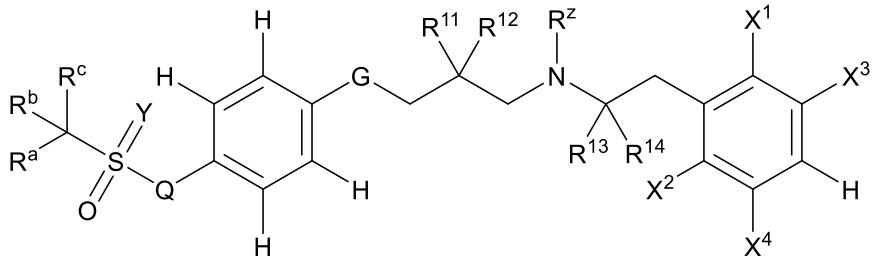
21. The compound of claim 17, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is of formula (II-E1):



(II-E1),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

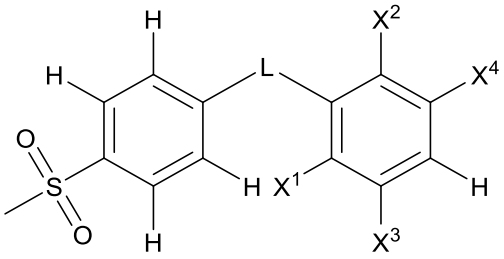
22. The compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein L is , such that the compound is of formula (III):



(III),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

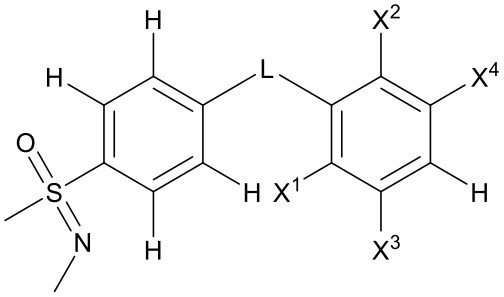
23. The compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q is absent, Y is O, and R^a, R^b, and R^c are each independently H, such that the compound is of formula (B-2):



(B-2),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

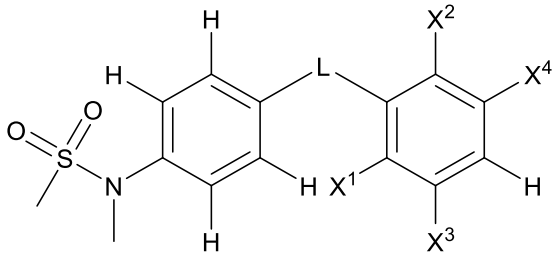
24. The compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q is absent, Y is -N(CH_3), and R^a, R^b, and R^c are each independently H, such that the compound is of formula (B-5):



(B-5),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

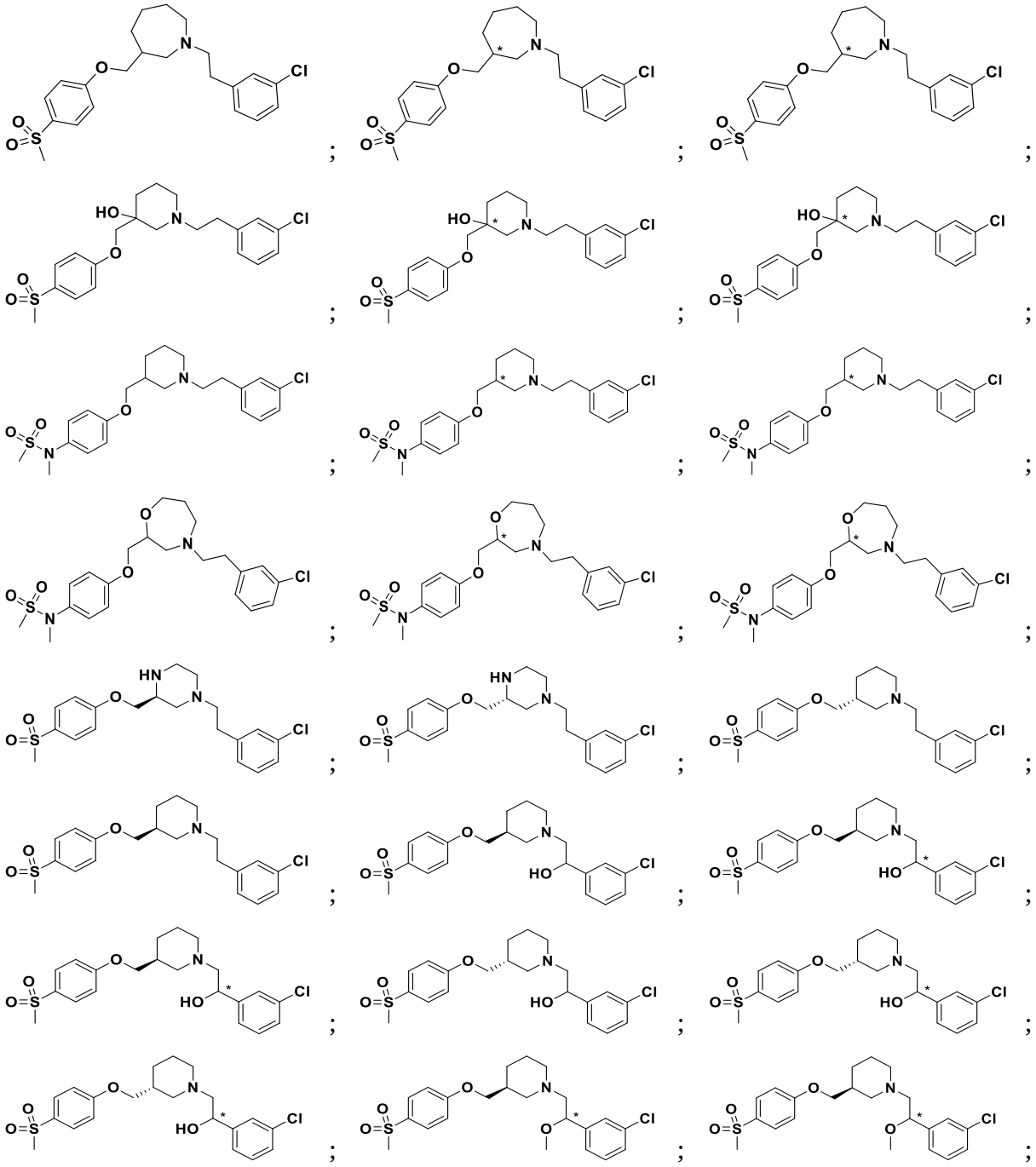
25. The compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q is -N(CH_3), Y is O, and R^a, R^b, and R^c are each independently H, such that the compound is of formula (C-1):

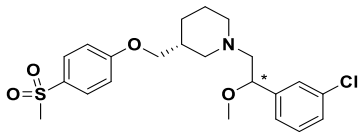
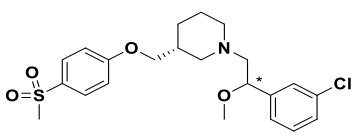
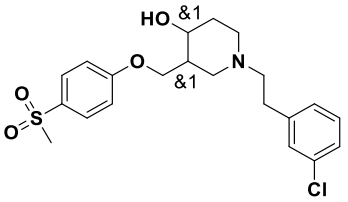
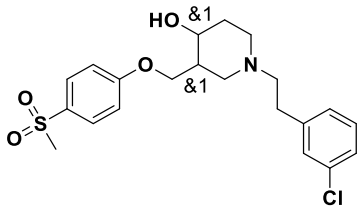
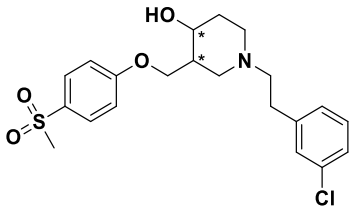
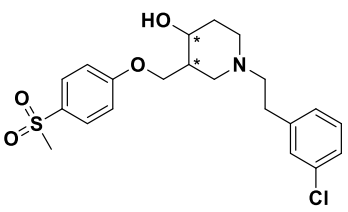
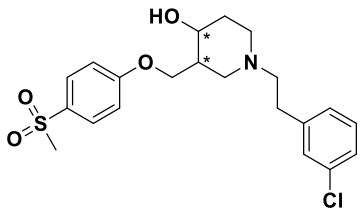
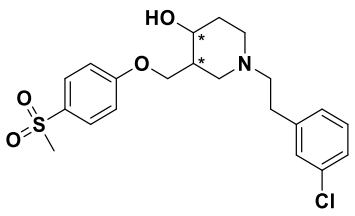
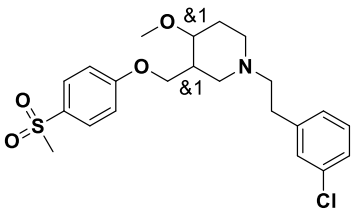
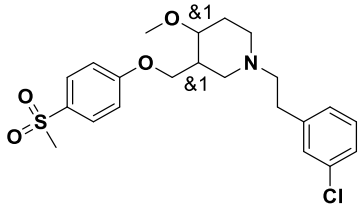
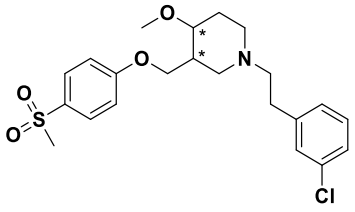
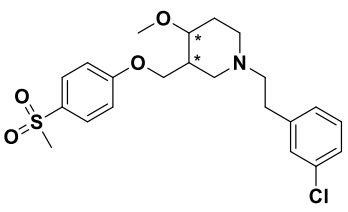
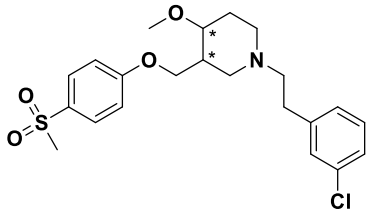
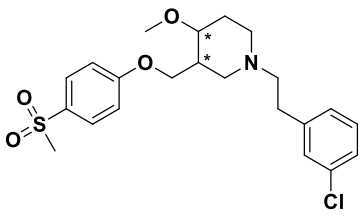
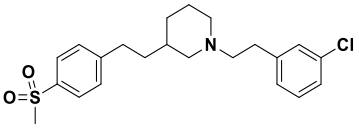
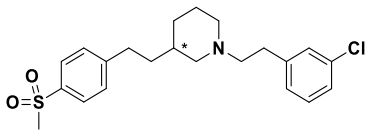
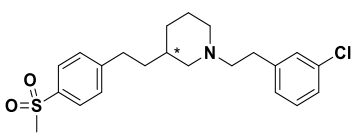
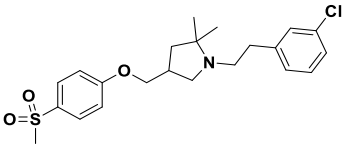
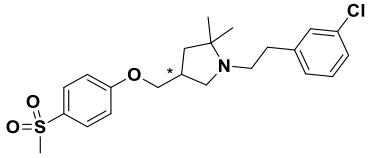
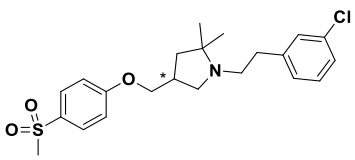
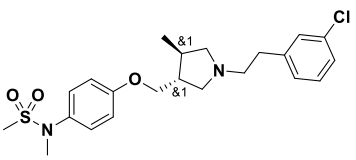
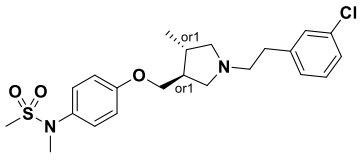
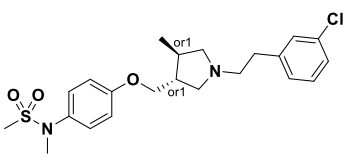
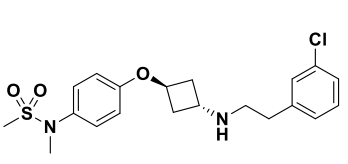


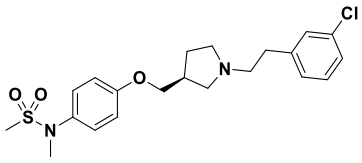
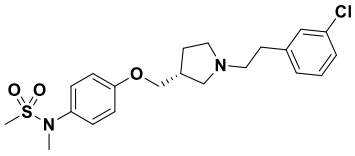
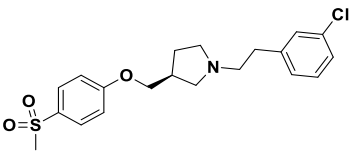
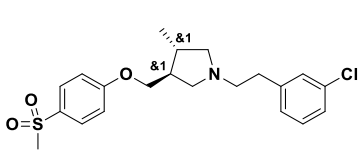
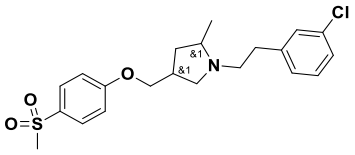
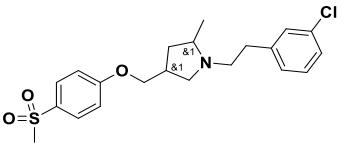
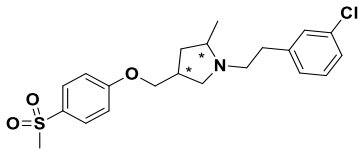
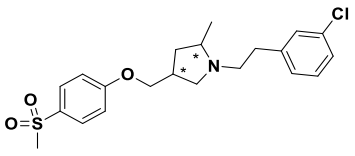
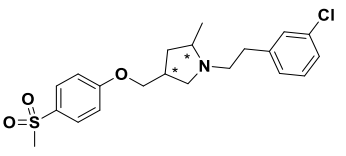
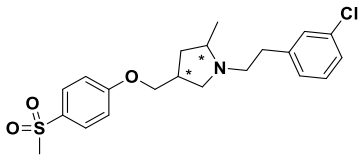
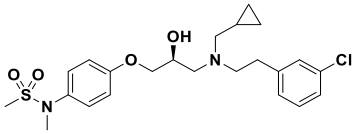
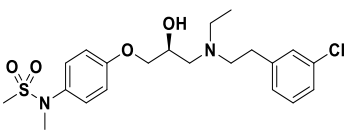
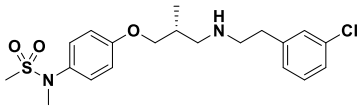
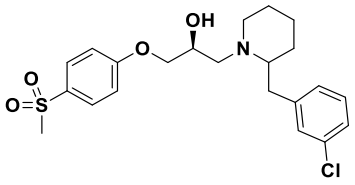
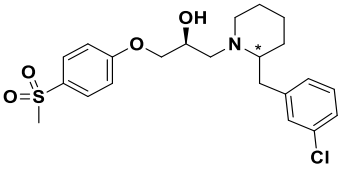
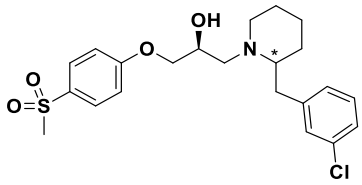
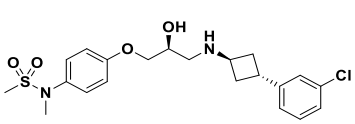
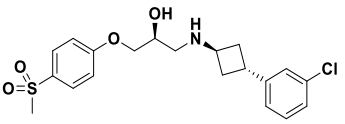
(C-1),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

26. The compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is selected from the group consisting of

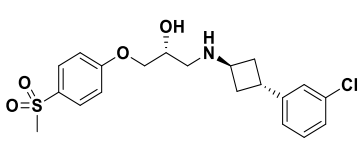
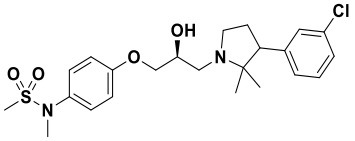
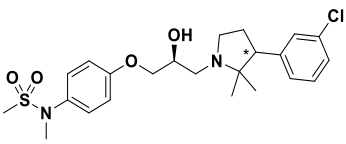
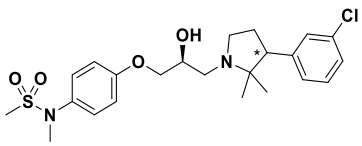
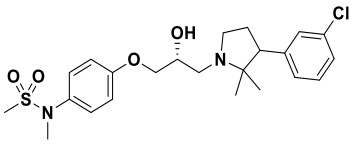
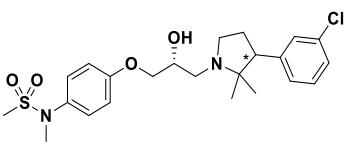
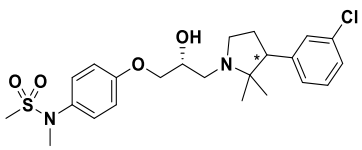
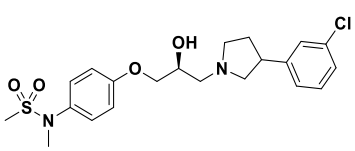
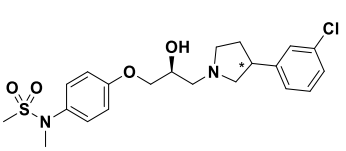
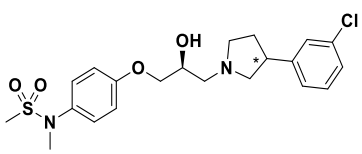
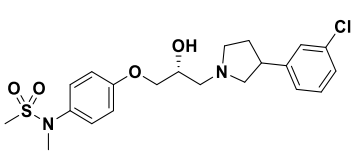
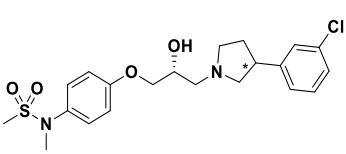


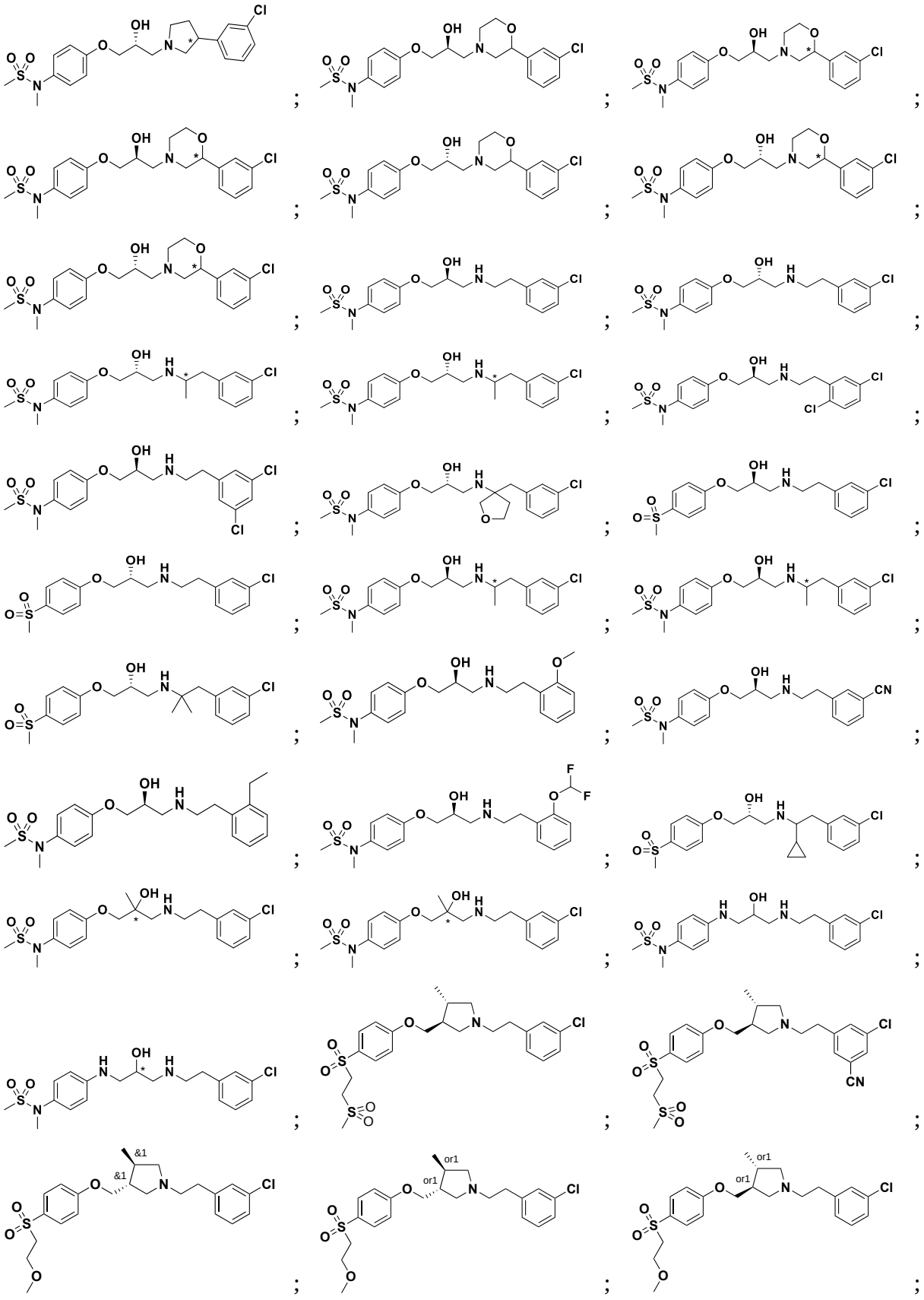

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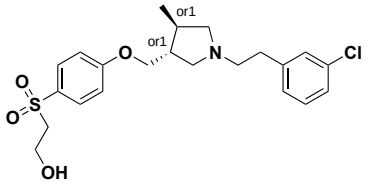
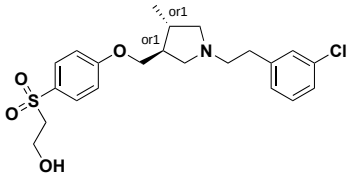
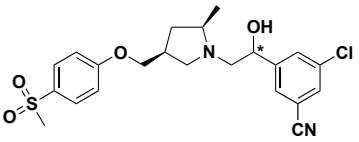
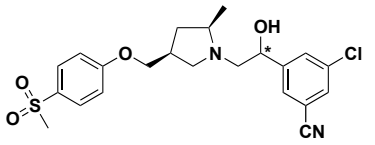
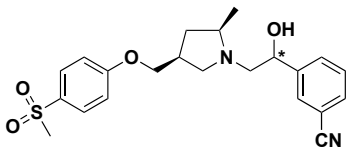
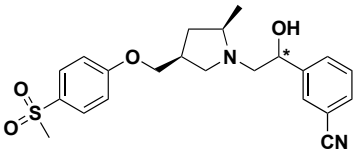
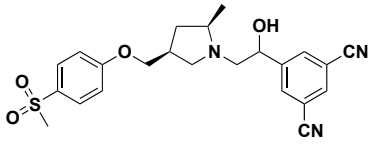
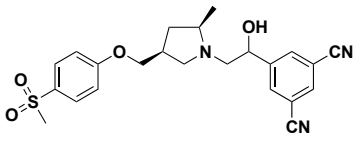
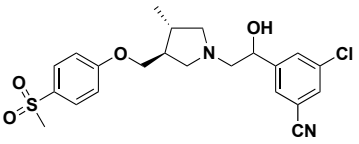
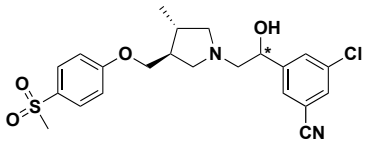
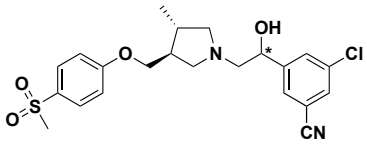
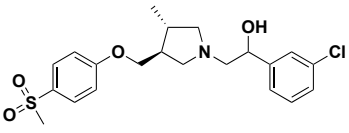
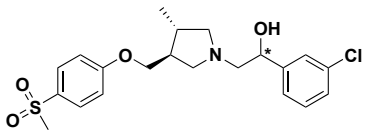
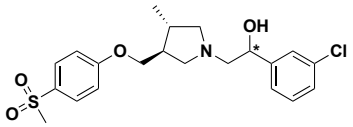
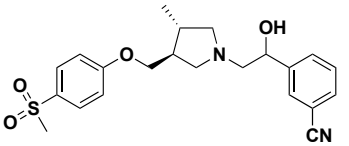
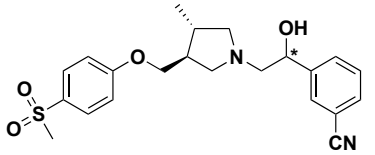
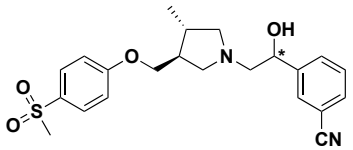
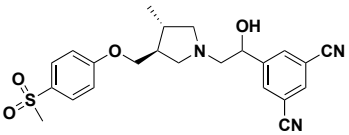
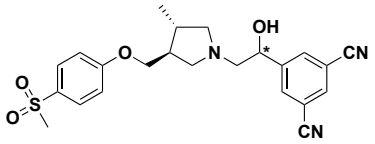
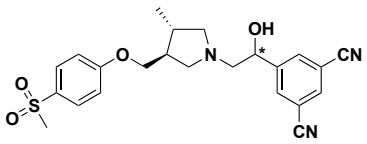
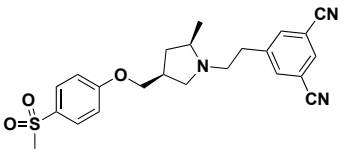
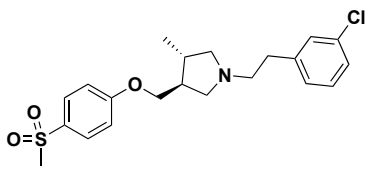
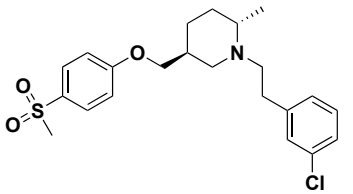
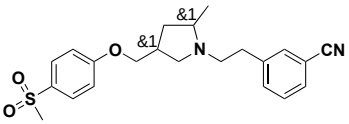
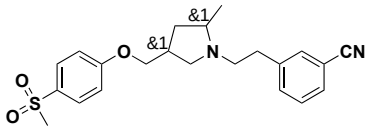
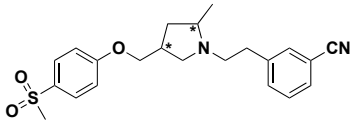
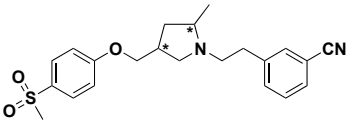
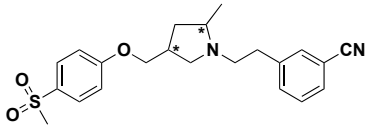
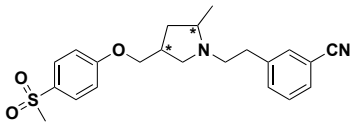
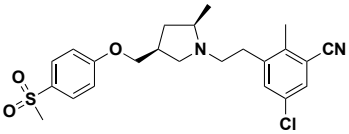

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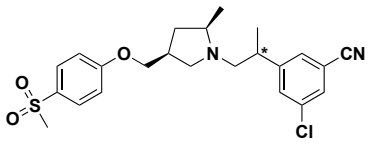
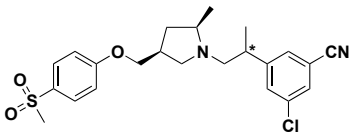
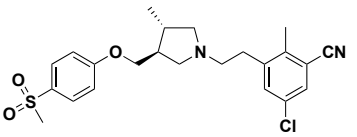
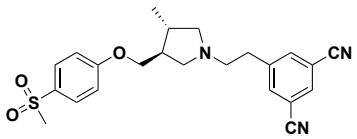
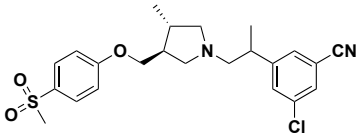
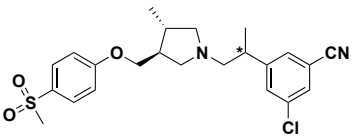
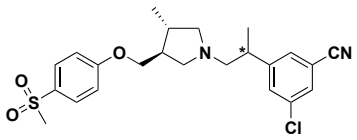
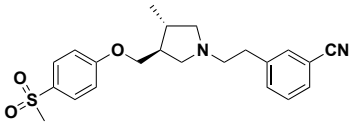
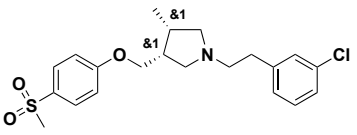
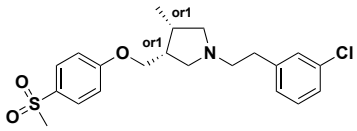
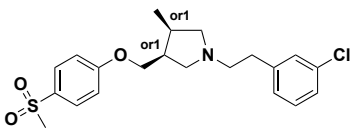
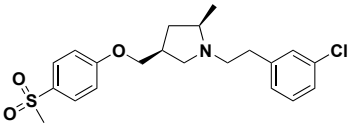
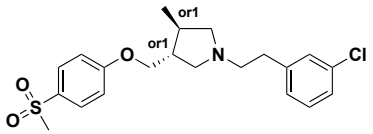
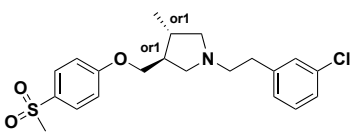
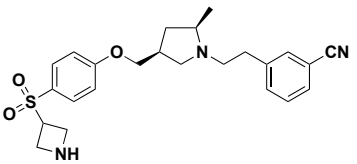
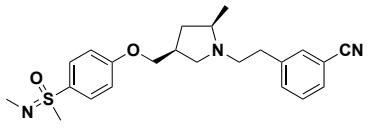
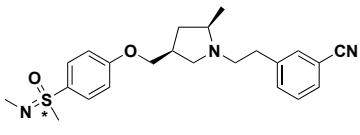
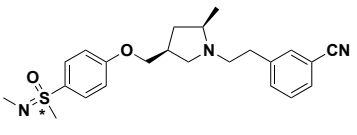
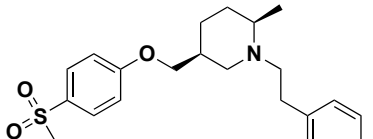
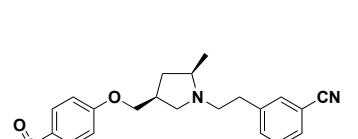
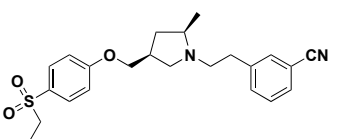
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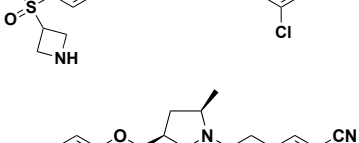
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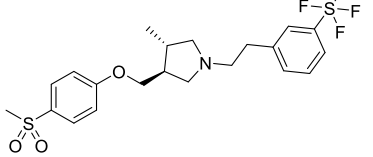
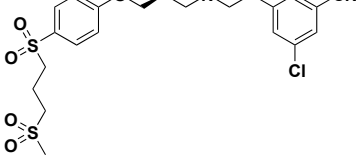
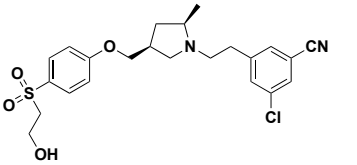
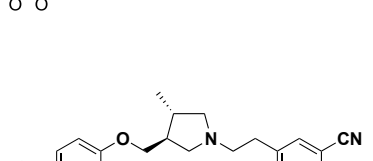
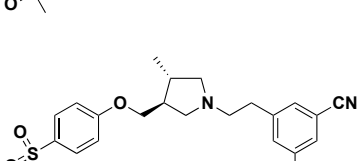
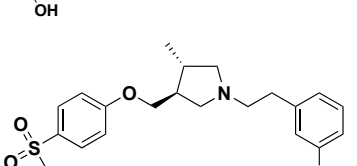
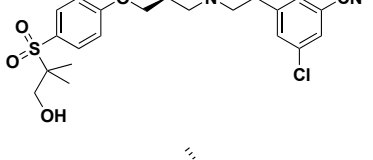
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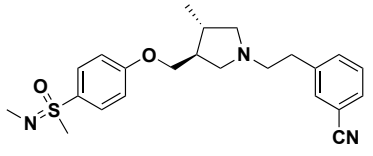
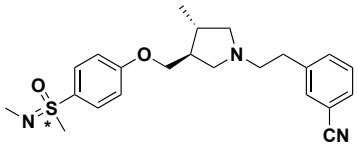
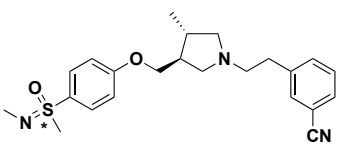

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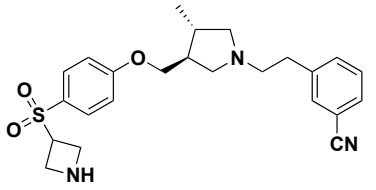
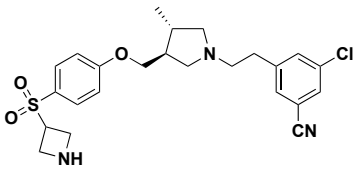
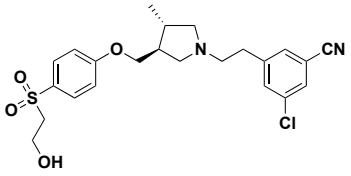
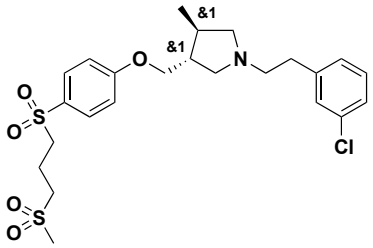
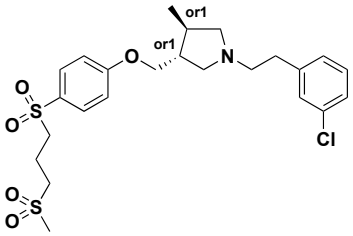
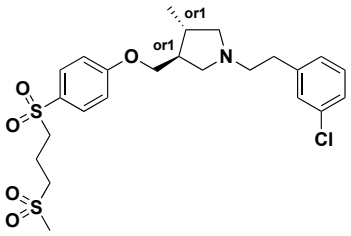
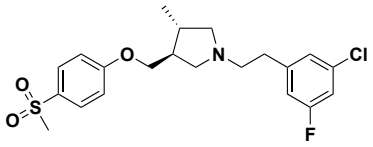
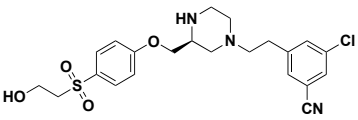
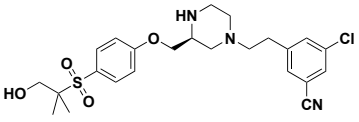
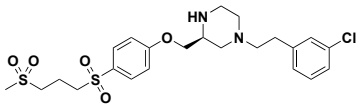
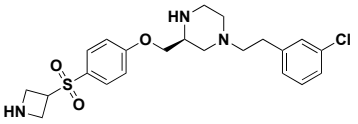
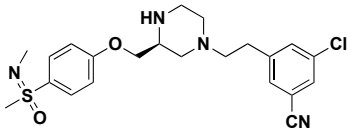
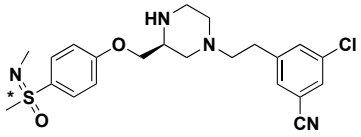
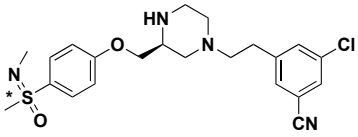
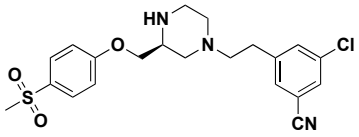
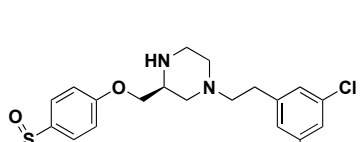
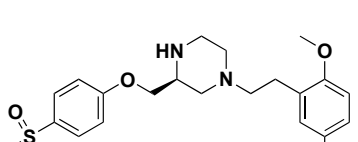
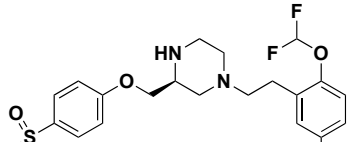

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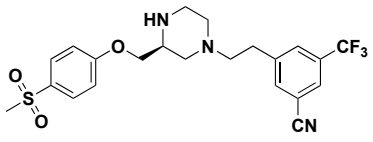
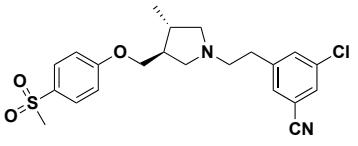
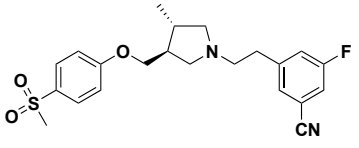
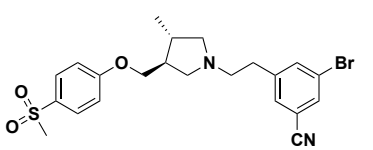
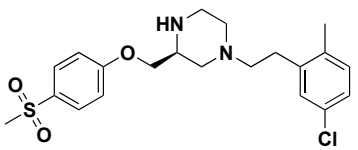
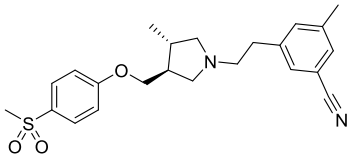
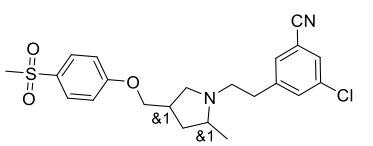
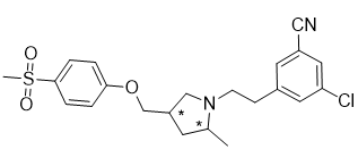
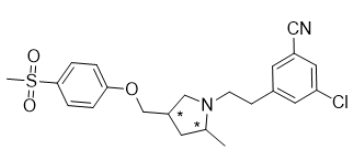
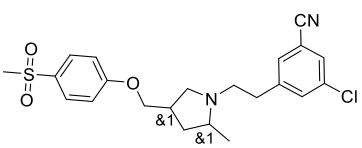
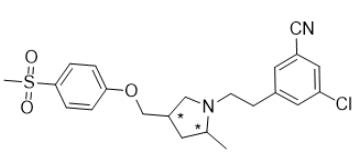
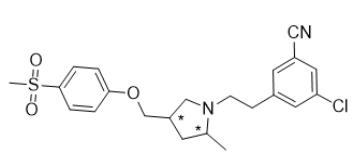
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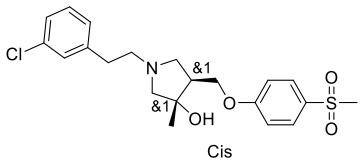
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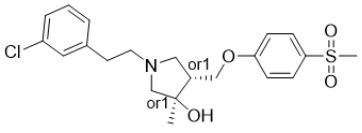
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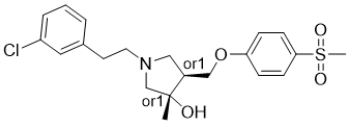



















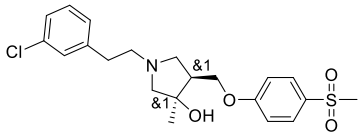













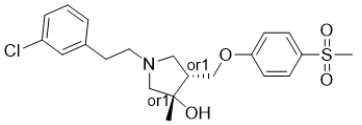


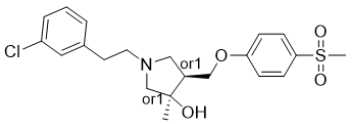


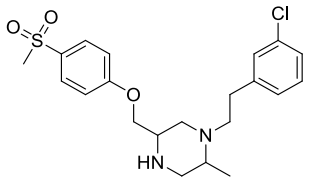
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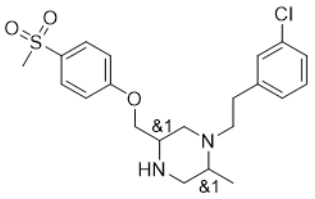
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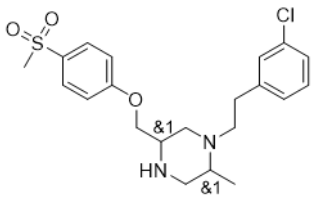
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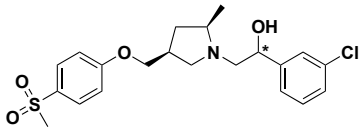
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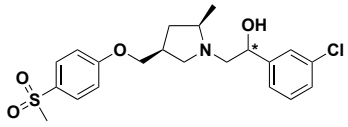
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or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

27. A pharmaceutical composition, comprising (i) a compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) one or more pharmaceutically acceptable excipients.

28. Use of a compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition of claim 27, in the manufacture of a medicament for modulating APOL1 in a cell.

29. Use of a compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition of claim 27, in the manufacture of a medicament for inhibiting APOL1 in a cell.

30. Use of a compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition of claim 27, in the manufacture of a medicament for treating an APOL1-mediated disease, disorder, or condition in an individual in need thereof.

31. The use of claim 30, wherein the disease, disorder, or condition is a kidney disease.

32. The use of claim 30, wherein the disease, disorder, or condition is a chronic kidney disease (CKD).

33. The use of claim 30, wherein the disease, disorder, or condition is selected from the group consisting of chronic kidney disease, focal segmental glomerulosclerosis (FSGS), hypertension-attributed kidney disease, human immunodeficiency virus-associated nephropathy (HIVAN), sickle-cell nephropathy, lupus nephritis, diabetic kidney disease, APOL1-associated nephropathy, viral nephropathy, COVID-19 associated nephropathy, preeclampsia, and sepsis.

34. Use of a compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition of claim 27, in the manufacture of a medicament for delaying the development of an APOL1-mediated disease, disorder, or condition.

35. The use of claim 30, wherein the individual has an APOL1 mutation.

36. The use of claim 35, wherein the APOL1 mutation is a gain-of-function mutation.

37. A kit, comprising (i) a compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition of claim 64, and (ii) instructions for use in treating an APOL1-mediated disease, disorder, or condition in an individual in need thereof.

38. A compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition of claim 27, for use in therapy.