APOL1 INHIBITORS AND METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application Serial No. 63/300,592, filed January 18, 2022, U.S. Provisional Application Serial No. 63/311,668, filed February 18, 2022, U.S. Provisional Application Serial No. 63/332,553, filed April 19, 2022, U.S. Provisional Application Serial No. 63/400,359, filed August 23, 2022, and U.S. Provisional Application Serial No. 63/422,341, filed November 3, 2022, each of which is hereby incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] Apolipoprotein L1 (APOL1) is a pore forming innate immunity factor, protecting individuals from trypanosome parasites (Vanhamme, L. et al. *Nature* (2003) 422, 83–87). The secreted form of APOL1 circulates in blood as part of distinct high-density lipoprotein (HDL) complexes, known as trypanosome lytic factors (TLFs) (Rifkin, M. R. *Proc. Natl. Acad. Sci. USA.* (1978) 75, 3450–3454; Raper, J. et al. *Infect. Immun.* (1999) 67, 1910–1916). TLFs are internalized by the parasites through endocytosis (Hager, K. M. et al. *J. Cell Biol.* (1994) 126, 155–167). Within trypanosomes, APOL1 forms cation pores, causing ion flux, swelling, and eventual lysis (Rifkin, M. R. *Exp. Parasitol.* (1984) 58, 81–93; Molina-Portela, M. P. et al. *Mol. Biochem. Parasitol.* (2005) 144, 218–226; Pérez-Morga, D. et al. *Science*. (2005) 309, 469–472; Thomson, R. & Finkelstein, A. *Proc. Natl. Acad. Sci. USA.* (2015) 112, 2894–2899).

[0003] Several *Trypanosoma brucei* subspecies (*T.b. rhodesiense* and *T.b. gambiense*) developed resistance mechanisms to APOL1-dependent killing (Pays, E. et al. *Nat. Rev. Microbiol.* (2014) 12, 575–584). Positive selection resulted in APOL1 variants, G1 (S342G, I384M) and G2 (N388Δ, Y389Δ), capable of interfering with these resistance mechanisms (Genovese, G. et al. *Science.* (2010) 329, 841–845). However, individuals with any binary combination of these variants (G1/G1, G2/G2, or G1/G2), have a greater risk of developing a variety of chronic kidney diseases, including focal segmental glomerulosclerosis (FSGS), hypertension-attributed kidney disease, human immunodeficiency virus-associated nephropathy (HIVAN) (Genovese, G. et al. *Science.* (2010) 329, 841–845; Tzur, S. et al. *Hum. Genet.* (2010) 128, 345-350; Kopp, J. B. et al. *J. Am. Soc. Nephrol.* (2011) 22, 2129–2137), sickle cell nephropathy (Ashley-Koch, A. E. et al. *Br. J. Haematol.* (2011) 155, 386–394), lupus nephritis (Freedman, B. I. et al. *Arthritis Rheumatol.* (2014) 66, 390–396), and an increased rate of

Glomerular Filtration Rate (GFR) decline in diabetic kidney disease (Parsa, A. et al. *N. Engl. J. Med.* (2013) 369, 2183–2196). The APOL1 high-risk genotype has also been associated with 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.

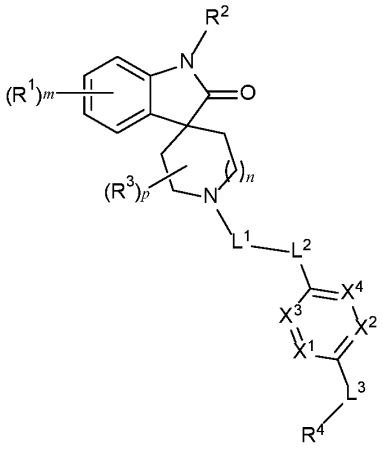
[0004] Numerous studies have shown that APOL1 risk variants are toxic when overexpressed in human cells (Wan, G. et al. *J. Biol. Chem.* (2008) 283, 21540–21549; Lan, X. et al. *Am. J. Physiol. Renal Physiol.* (2014) 307, F326–F336; Olabisi, O. A. et al. *Proc. Natl. Acad. Sci. USA.* (2016) 113, 830–837; 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 OF THE INVENTION

[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 treat other APOL1-mediated disorders such as preeclampsia and sepsis. Additionally, for individuals with the APOL1 high-risk genotype, the disclosed compounds and may prevent the onset of non-diabetic renal disease and/or delaying the progression of any form of chronic kidney disease. The disclosed chemical

matter may also prevent and/or delay progressive renal allograft loss in patients who have received a kidney transplant from a high-risk APOL1 genotype donor.

[0006] In one aspect, provided is a compound of formula (II):



(II),

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

m is an integer from 0 to 4;

n is an integer from 0 to 2;

p is an integer from 0 to 10;

R^1, if present is, independently at each occurrence selected from the group consisting of halo, -CN, C_{1-6}alkoxy, and C_{1-6}alkyl, wherein

the C_{1-6}alkoxy of R^1 is optionally substituted with one or more halo, and

the C_{1-6}alkyl of R^1 is optionally substituted with one or more halo;

R^2 is H, C_{1-6}alkyl, C_{3-10}cycloalkyl, or 3-15 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^2 is optionally substituted with one or more deuterium, halo, -OH, $-NH_2$, or C_{1-6}alkoxy, and

the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more -OH;

R^3, if present, is C_{1-6}alkyl;

L^1 is C_{1-6}alkylene, wherein

the C_{1-6}alkylene of L^1 is optionally substituted with one or more deuterium or C_{1-6}alkyl, and wherein

the C_{1-6}alkyl is further optionally substituted with one or more -OH or C_{1-6}alkoxy;

L^2 is O or $N(R^x)$, wherein R^x is H or C_{1-6}alkyl; and

either

(1) L^3 is absent or is O, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or C_{1-6}alkylene, wherein

the C_{3-10}cycloalkyl of L^3 is optionally substituted with one or more –OH or C_{1-6}alkyl,

the C_{1-6}alkylene of L^3 is optionally substituted with one or more –OH or C_{1-6}alkyl, wherein

the C_{1-6}alkyl is optionally substituted with one or more -OH, and

the 3-10 membered heterocyclyl of L^3 is optionally substituted with one or more –OH or C_{1-6}alkyl;

X^1 and X^2 are each independently N or $C(R^5)$; and

R^4 is:

(i) $-S(O)_2-R^a$;

(ii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^4 is optionally substituted with one or more C_{1-6}alkyl;

(iii) $-N(R^d)_2$, wherein R^d is independently at each occurrence H, C_{1-6} alkyl, or $-S(O)_2-R^a$, wherein

the C_{1-6}alkyl of R^d is optionally substituted with one or more -OH,

(iv) $-NS(O)-(C_{1-6}alkyl)_2$, wherein the C_{1-6}alkyl is optionally substituted with one or more –OH,

(v) $-C(O)-N(R^e)_2$ wherein R^e is independently at each occurrence H, C_{1-6} alkyl, or 3-10 membered heterocycle, wherein

the 3-10 membered heterocycle of R^e is optionally substituted with one or more oxo, or both R^e together with the N to which they are attached are taken together to form a 3-10 membered heterocyclyl, wherein

the 3-10 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, $-NH-S(O)_2-R^a$, or $-S(O)_2-R^a$,

(vi) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl, -OH , oxo or $-S(O)_2R^a$,

(vii) $-S(O)-N(C_{1-6}alkyl)-(C_{1-6}alkyl)$,

(viii) -CN,

(ix) $-(CH_2)_qOH$, wherein q is an integer from 0-6,

(x) $-C(O)-C_{1-6}$alkyl, or

(xi) $-P(O)(C_{1-6}alkyl)_2$;

or

(2) L^3 is absent; and

one of X^1 and X^2 is N or $C(R^5)$; and

the other of X^1 and X^2 is N or C that is taken together with R^4, and the atoms to which they are attached, to form a 5-10 membered heterocyclyl or a 5-20 membered heteroaryl, wherein

the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein

R^b is, independently at each occurrence, selected from the group consisting of -OH, halo, oxo, C_{1-6}alkyl, $-C(O)-C_{1-6}$alkyl, $-C(O)-NH_2$, $-C(O)-NH(C_{1-6}alkyl)$, $-C(O)-N(C_{1-6}alkyl)_2$, $-S(O)_2-R^a$, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, OH, $-S(O)_2-C_{1-6}$alkyl, or C_{3-10}cycloalkyl, and wherein

the C_{3-10}cycloalkyl of the C_{1-6}alkyl of R^b is further optionally substituted with one or more C_{1-6}alkyl or -OH and

the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more -OH, C_{3-10}cycloalkyl, or C_{1-6}alkyl, and wherein

the C_{1-6}alkyl of the C_{3-10}cycloalkyl of R^b is further optionally substituted with one or more -OH, deuterium, or halo, and

the 5-20 membered heteroaryl is optionally substituted with one or more R^c, wherein

R^c is, independently at each occurrence, selected from the group consisting of halo, C_{1-6}alkyl, $-C(O)-C_{1-6}$alkyl, $-C(O)-NH_2$, $-C(O)-NH(C_{1-6}alkyl)$, $-C(O)-N(C_{1-6}alkyl)_2$, $-S(O)_2-R^a$, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more $-S(O)_2-C_{1-6}$alkyl,

the C_{3-10}cycloalkyl of R^c is optionally substituted with one or more -OH or C_{1-6}alkyl, and

the 3-10 membered heterocyclyl of R^c is optionally substituted with one or more -OH or C_{1-6}alkyl, and wherein

the C_{1-6}alkyl of the 3-10 membered heterocyclyl of R^c is further optionally substituted with one or more -OH;

R^a is, independently at each occurrence:

(i) C_{1-6}alkyl optionally substituted with one or more halo, -OH, -$S(O)_2$-C_{1-6}alkyl, or -N(C_{1-6}alkyl)-C(O)-C_{1-6}alkyl,

(ii) C_{3-10}cycloalkyl optionally substituted with one or more -OH, -$C(O)_2$-C_{1-6}alkyl, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, or –C(O)-C_{3-10}heterocyclyl, or C_{1-6}alkyl, wherein

the C_{1-6}alkyl is optionally substituted with one or more -OH,

(iii) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl, or

(iv) NH(C_{1-6}alkyl);

R^5 is, independently at each occurrence, H, halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein

the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo or -OH, and

the C_{1-6}alkoxy of R^5 is optionally substituted with one or more halo;

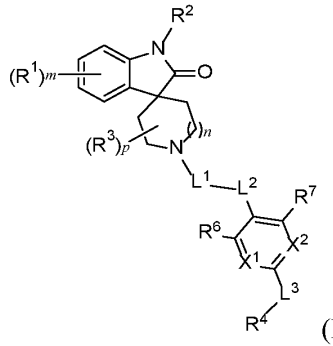
X^3 is N or C(R^6);

X^4 is N or C(R^7);

and

R^6 and R^7 are each independently H or halo.

[0007] In one aspect, provided is a compound of formula (I'):



(I'),

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

m is an integer from 0 to 4;

n is an integer from 0 to 2;

p is an integer from 0 to 10;

R^1, if present is, independently at each occurrence selected from the group consisting of halo, -CN, C_{1-6}alkoxy, or C_{1-6}alkyl, wherein

the C_{1-6}alkoxy of R^1 is optionally substituted with one or more halo, and

the C_{1-6}alkyl of R^1 is optionally substituted with one or more halo;

R^2 is H, C_{1-6}alkyl, C_{3-10}cycloalkyl, or 3-15 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^2 is optionally substituted with one or more halo, -OH, $-NH_2$, or C_{1-6}alkoxy, and

the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more -OH;

R^3, if present, is C_{1-6}alkyl;

L^1 is C_{1-6}alkylene, wherein the C_{1-6}alkylene of L^1 is optionally substituted with one or more C_{1-6}alkyl, and wherein the C_{1-6}alkyl is further optionally substituted with one or more -OH or C_{1-6}alkoxy;

L^2 is O or $N(R^x)$, wherein R^x is H or C_{1-6}alkyl; and

either

(1) L^3 is absent or is O, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or C_{1-6}alkylene, wherein

the C_{3-10}cycloalkyl is optionally substituted with one or more -OH or C_{1-6}alkyl,

the C_{1-6}alkylene of L^3 is optionally substituted with one or more -OH or C_{1-6}alkyl, and

the 3-10 membered heterocyclyl is optionally substituted with one or more –OH;

X^1 and X^2 are each independently N or $C(R^5)$; and

R^4 is:

(i) $-S(O)_2-R^a$;

(ii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^4 is optionally substituted with one or more C_{1-6}alkyl;

(iii) $-N(R^d)_2$, wherein R^d is independently at each occurrence H, C_{1-6} alkyl, or $-S(O)_2-R^a$, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more -OH,

(iv) $-NS(O)-(C_{1-6}alkyl)_2$, wherein the C_{1-6}alkyl is optionally substituted with one or more -OH,

(v) $-C(O)-N(R^e)_2$ wherein R^e is independently at each occurrence H, C_{1-6} alkyl, or 3-10 membered heterocycle, wherein the 3-10 membered heterocycle is optionally substituted with one or more oxo, or both R^e together with the N to which they

are attached are taken together to form a 3-10 membered heterocyclyl, wherein the 3-10 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, -NH-$S(O)_2$-R^a, or -$S(O)_2$-R^a,

(vi) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl, -OH , oxo, or -$S(O)_2R^a$,

(vii) -S(O)-N(C_{1-6}alkyl)-(C_{1-6}alkyl),

(viii) -CN,

(ix) -$(CH_2)_q$OH, wherein q is an integer from 0-6,

(x) -C(O)-C_{1-6}alkyl, or

(xi) -P(O)(C_{1-6}alkyl)$_2$;

or

(2) L^3 is absent; and

one of X^1 and X^2 is N or C(R^5); and

the other of X^1 and X^2 is N or C that is taken together with R^4 and the atoms to which they are attached to form a 5-10 membered heterocyclyl or a 5-20 membered heteroaryl, wherein

the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is, independently at each occurrence, selected from the group consisting of halo, oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -$S(O)_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, OH, -$S(O)_2$-C_{1-6}alkyl, or C_{3-10}cycloalkyl, and

wherein the C_{3-10}cycloalkyl of the C_{1-6}alkyl of R^b is further optionally substituted with one or more C_{1-6}alkyl or -OH and

the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more -OH, C_{3-10}cycloalkyl, or C_{1-6}alkyl, and

wherein the C_{1-6}alkyl of the C_{3-10}cycloalkyl of R^b is further optionally substituted with one or more –OH, and

the 5-20 membered heteroaryl is optionally substituted with one or more R^c, wherein R^c is, independently at each occurrence, selected from the group consisting of halo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -$S(O)_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more -$S(O)_2$-C_{1-6}alkyl,

the C_{3-10}cycloalkyl of R^c is optionally substituted with one or more –OH or C_{1-6}alkyl,

and the 3-10 membered heterocyclyl of R^c is optionally substituted with one or more -OH or C_{1-6}alkyl, and

wherein the C_{1-6}alkyl of the 3-10 membered heterocyclyl of R^c is further optionally substituted with one or more -OH;

R^a is, independently at each occurrence:

(i) C_{1-6}alkyl optionally substituted with one or more halo, -OH, -$S(O)_2$-C_{1-6}alkyl, or -N(C_{1-6}alkyl)-C(O)-C_{1-6}alkyl,

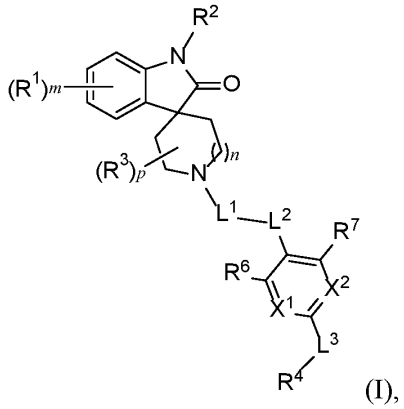
(ii) C_{3-10}cycloalkyl optionally substituted with one or more -OH, -$C(O)_2$-C_{1-6}alkyl, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, or –C(O)-C_{3-10}heterocyclyl, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more -OH, or

(iii) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl;

R^5 is, independently at each occurrence, H, halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH and wherein the C_{1-6}alkoxy of R^5 is optionally substituted with one or more halo; and

R^6 and R^7 are each independently H or halo.

[0008] In one aspect, provided is a compound of formula (I):



(I),

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

m is an integer from 0 to 4;

n is an integer from 0 to 2;

p is an integer from 0 to 10;

R^1 if present is, independently at each occurrence, selected from the group consisting of halo, -CN, C_{1-6}alkoxy or -C_{1-6}alkyl, wherein

the C_{1-6}alkoxy of R^1 is optionally substituted with one or more halo, and

the C_{1-6}alkyl of R^1 is optionally substituted with one or more halo;

R^2 is H, C_{1-6}alkyl, C_{3-10}cycloalkyl, or 3-15 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^2 is optionally substituted with one or more halo, -OH, -NH_2, or C_{1-6}alkoxy, and

the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more -OH;

R^3, if present, is C_{1-6}alkyl;

L^1 is C_{1-6}alkylene, wherein the C_{1-6}alkylene of L^1 is optionally substituted with one or more C_{1-6}alkyl, and wherein the C_{1-6}alkyl is further optionally substituted with one or more -OH or C_{1-6}alkoxy;

L^2 is O or N(R^x), wherein R^x is H or C_{1-6}alkyl; and

either

(1) L^3 is absent or is O, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or C_{1-6}alkylene, wherein

the C_{1-6}alkylene of L^3 is optionally substituted with one or more C_{1-6}alkyl, and

the 3-10 membered heterocyclyl is optionally substituted with one or more –OH;

X^1 and X^2 are each independently N or C(R^5); and

R^4 is:

(i) -$S(O)_2$-R^a,

(ii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^4 is optionally substituted with one or more C_{1-6}alkyl,

(iii) -N(R^d)$_2$, wherein R^d is independently at each occurrence H, C_{1-6} alkyl, or -$S(O)_2$-R^a, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more –OH,

(iv) -NS(O)-(C_{1-6}alkyl)$_2$, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more –OH,

(v) -C(O)-N(R^e)$_2$ wherein R^e is independently at each occurrence H, C_{1-6} alkyl, or 3-10 membered heterocycle, wherein the 3-10 membered heterocycle is optionally substituted with one or more oxo, or both R^e together with the N to which they

are attached are taken together to form a 3-10 membered heterocyclyl, wherein the 3-10 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, NH-$S(O)_2$-R^a, or -$S(O)_2$-R^a,

(vi) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl or oxo,

(vii) -S(O)-N(C_{1-6}alkyl)-(C_{1-6}alkyl), or

(viii) –CN;

or

(2) L^3 is absent; and

one of X^1 and X^2 is N or C(R^5); and

the other of X^1 and X^2 is N or C that is taken together with R^4, and the atoms to which they are attached, to form a 5-10 membered heterocyclyl or a 5-20 membered heteroaryl, wherein

the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is, independently at each occurrence, selected from the group consisting of halo, oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -$S(O)_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, OH, or -$S(O)_2$-C_{1-6}alkyl, and

the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more -OH, and

the 5-20 membered heteroaryl is optionally substituted with one or more R^c, wherein R^c is, independently at each occurrence, selected from the group consisting of halo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -$S(O)_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more -$S(O)_2$-C_{1-6}alkyl, and

the C_{3-10}cycloalkyl of R^c is optionally substituted with one or more -OH;

R^a is, independently at each occurrence:

(i) C_{1-6}alkyl optionally substituted with one or more halo, -OH, -$S(O)_2$-C_{1-6}alkyl, or -N(C_{1-6}alkyl)-C(O)-C_{1-6}alkyl, or

(ii) C_{3-10}cycloalkyl optionally substituted with one or more -OH, -$C(O)_2$-C_{1-6}alkyl, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$,–C(O)-C_{3-10}heterocyclyl, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more -OH, or

(iii) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl;

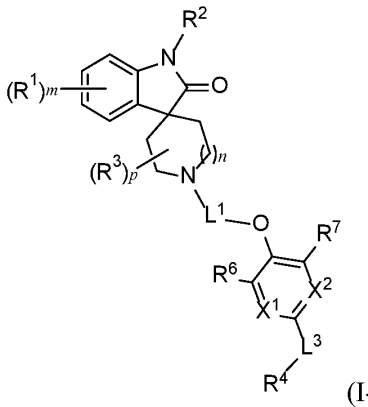
R^5 is, independently at each occurrence, H, halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo or -OH, and wherein the C_{1-6}alkoxy is optionally substituted with one or more halo; and

R^6 and R^7 are each independently H or halo.

[0009] Any embodiments provided herein of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof, are also embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0010] Any embodiments provided herein of a compound of formula (I) or (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof, are also embodiments of a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0011] In one aspect, provided herein is a compound of formula (I-A):

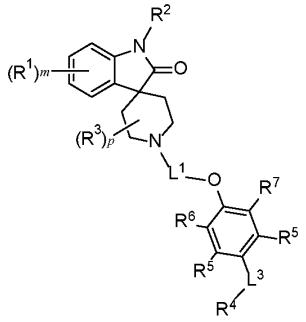


(I-A),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein: *n* is 1 or 2; and wherein *m*, *p*, R^1, R^2, R^3, L^1, L^3, R^4, X^1, X^2, R^6, and R^7 are as defined elsewhere herein. In another variation, *m*, *p*, R^1, R^2, R^3, L^1, L^3, R^4, X^1, X^2, R^6, and R^7 of formula (I-A) are as defined for a compound of formula (I'), or (II), or a stereoisomer or

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

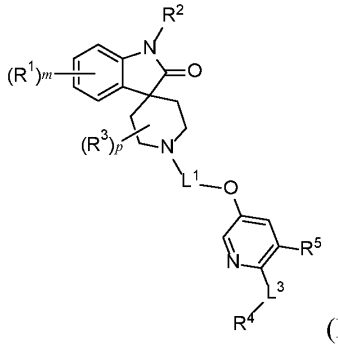
[0012] In one aspect, provided herein is a compound of formula (I-B):



(I-B),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein: m, p, R^1, R^2, R^3, L^1, L^3, R^4, R^5, R^6, and R^7 are as defined elsewhere herein. In another variation, m, p, R^1, R^2, R^3, L^1, L^3, R^4, R^5, R^6, and R^7 of formula (I-B) are as defined for a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

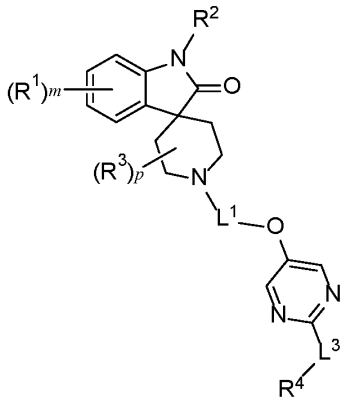
[0013] In one aspect, provided herein is a compound of formula (I-C):



(I-C),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein m, p, R^1, R^2, R^3, L^1, L^3, R^4, and R^5 are as defined elsewhere herein. In another variation, m, p, R^1, R^2, R^3, L^1, L^3, R^4, and R^5 of formula (I-C) are as defined for a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

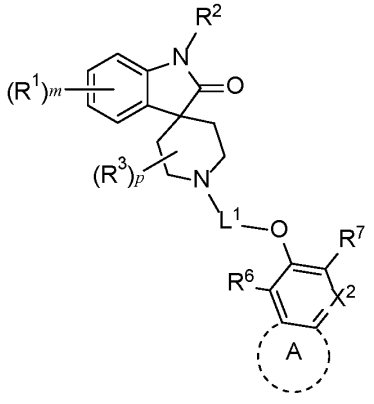
[0014] In one aspect, provided herein is a compound of formula (I-D):



(I-D),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein *m*, *p*, R^1, R^2, R^3, L^1, L^3, and R^4 are as defined elsewhere herein. In another variation, *m*, *p*, R^1, R^2, R^3, L^1, L^3, and R^4 of formula (I-D) are as defined for a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

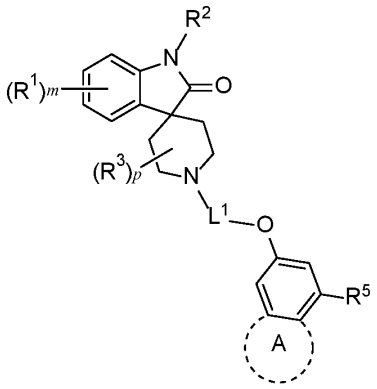
[0015] In one aspect, provided herein is a compound of formula (I-E):



(I-E),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein *m*, *p*, R^1, R^2, R^3, L^1, X^2, R^6, R^7, and ring A are as defined elsewhere herein. In another variation, *m*, *p*, R^1, R^2, R^3, L^1, X^2, R^6, R^7, and ring A of formula (I-E) are as defined for a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

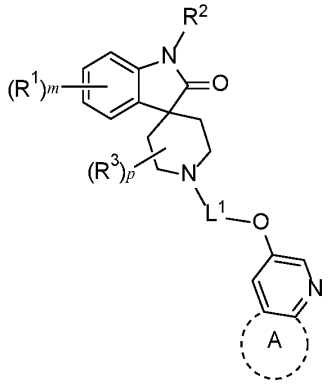
[0016] In one aspect, provided herein is a compound of formula (I-F):



(I-F),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein *m*, *p*, R^1, R^2, R^3, L^1, R^5, and ring A are as defined elsewhere herein. In another variation, *m*, *p*, R^1, R^2, R^3, L^1, R^5, and ring A of formula (I-F) are as defined for a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

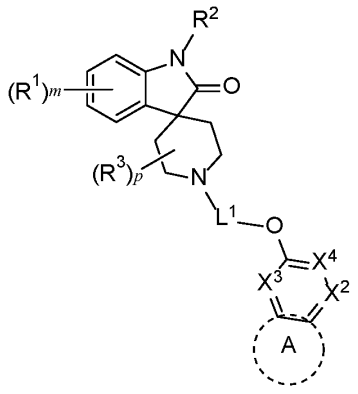
[0017] In one aspect, provided herein is a compound of formula (I-G):



(I-G),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein *m*, *p*, R^1, R^2, R^3, L^1, and ring A are as defined elsewhere herein. In another variation, *m*, *p*, R^1, R^2, R^3, L^1, and ring A of formula (I-G) are as defined for a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0018] In one aspect, provided herein is a compound of formula (II-A):



(II-A),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein *m*, *p*, R^1, R^2, R^3, L^1, X^2, X^3, X^4, and ring A are as defined elsewhere herein.

[0019] In one aspect, provided herein is a pharmaceutical composition, comprising (i) a compound of formula (I), or any embodiment or variation thereof, such as a compound of formula (I), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), or (I-G), 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 (I'), or any embodiment or variation thereof, such as a compound of formula (I), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), or (I-G), 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 (II), or any embodiment or variation thereof, such as a compound of formula (I), (I'), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), or (II-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) one or more pharmaceutically acceptable excipients.

[0020] In one aspect, 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 (I), or any embodiment or variation thereof, such as a compound of formula (I), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), or (I-G), 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 (I), or any embodiment or variation thereof, such as a compound of formula (I), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), or (I-G), 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 (I'), or any embodiment or variation thereof, such as a compound of formula (I), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), or (I-G), 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 (I'), or any embodiment or variation thereof, such as a compound of formula (I), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), or (I-G), 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 (II), or any embodiment or variation thereof, such as a compound of formula (I), (I'), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), or (II-A), 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 (II), or any embodiment or variation thereof, such as a compound of formula (I), (II), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), or (II-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) one or more pharmaceutically acceptable excipients.

[0021] In one aspect, 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 (I), or any embodiment or variation thereof, such as a compound of formula (I), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), or (I-G), 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 (I), or any embodiment or variation thereof, such as a compound of formula (I), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), or (I-G), 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 (I'), or any embodiment or variation thereof, such as a compound of formula (I), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), or (I-G), 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 (I), or any embodiment or variation thereof, such as a

compound of formula (I), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), or (I-G), 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 (II), or any embodiment or variation thereof, such as a compound of formula (I), (I'), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), or (II-A), 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 (II), or any embodiment or variation thereof, such as a compound of formula (I), (I'), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), or (II-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) one or more pharmaceutically acceptable excipients.

[0022] In one aspect, 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 (I), or any embodiment or variation thereof, such as a compound of formula (I), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), or (I-G), 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 (I), or any embodiment or variation thereof, such as a compound of formula (I), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), or (I-G), 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 vatiation, 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 (I'), or any embodiment or variation thereof, such as a compound of formula (I), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), or (I-G), 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 (I'), or any embodiment or variation thereof, such as a compound of formula (I), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), or (I-G), 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 vatiation, 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 (II), or any embodiment or variation thereof, such as a compound of formula (I), (I'), (I-A) (I-B), (I-C),

(I-D), (I-E), (I-F), (I-G), or (II-A), 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 (II), or any embodiment or variation thereof, such as a compound of formula (I), (I'), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), or (II-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) one or more pharmaceutically acceptable excipients.

[0023] In one aspect, provided herein is a kit, comprising (i) a compound of formula (I), or any embodiment or variation thereof, such as a compound of formula (I), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), or (I-G), 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 (I'), or any embodiment or variation thereof, such as a compound of formula (I), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), or (I-G), 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 (II), or any embodiment or variation thereof, such as a compound of (I), (I'), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), or (II-A), 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.

[0024] In some aspect, provided herein are methods of preparing a compound of formula (I), or any embodiment or variation thereof, such as a compound of formula (I), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), or (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing. In another variation, provided herein are methods of preparing a compound of formula (I'), or any embodiment or variation thereof, such as a compound of formula (I), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), or (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing. In another variation, provided herein are methods of preparing a compound of formula (I'), or any embodiment or variation thereof, such as a compound of formula of (I), (I'), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), or (II-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

DETAILED DESCRIPTION OF THE INVENTION

[0025] Unless clearly indicated otherwise, the terms "a," "an," and the like, refer to one or more.

[0026] 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.

[0027] "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.

[0028] 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 disease or condition, and may or may not have displayed detectable disease prior to the treatment methods described herein. "At risk" denotes that an individual has one or more so-called risk factors, which are measurable parameters that correlate with development of a disease or condition and are known in the art. An individual having one or more of these risk factors has a higher probability of developing the disease or condition than an individual without these risk factor(s).

[0029] "Treatment" or "treating" is an approach for obtaining beneficial or desired results including clinical results. Beneficial or desired results may include one or more of the following: decreasing one or more symptom resulting from the disease or condition; diminishing the extent of the disease or condition; slowing or arresting the development of one or more symptom associated with the disease or condition (*e.g.*, stabilizing the disease or condition, preventing or delaying the worsening or progression of the disease or condition); and relieving the disease, such as by causing the regression of clinical symptoms (*e.g.*, ameliorating the disease state, enhancing the effect of another medication, delaying the progression of the disease, increasing the quality of life, and/or prolonging survival).

[0030] As used herein, "delaying" development of a disease or condition means to defer, hinder, slow, retard, stabilize and/or postpone development of the disease or condition. This delay can be of varying lengths of time, depending on the history of the disease and/or individual being treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the individual does not develop the disease or condition.

[0031] As used herein, the term "therapeutically effective amount" or "effective amount" intends such amount of a compound of the disclosure or a pharmaceutically salt thereof sufficient to effect treatment when administered to an individual. As is understood in the art, an

effective amount may be in one or more doses, *e.g.*, a single dose or multiple doses may be required to achieve the desired treatment endpoint. An effective amount may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable or beneficial result may be or is achieved.

[0032] As used herein, "unit dosage form" refers to physically discrete units, suitable as unit dosages, each unit containing a predetermined quantity of active ingredient, or compound, which may be in a pharmaceutically acceptable carrier.

[0033] As used herein, by "pharmaceutically acceptable" is meant a material that is not biologically or otherwise undesirable, *e.g.*, the material may be incorporated into a pharmaceutical composition administered to an individual without causing significant undesirable biological effects.

[0034] The term "alkyl", as used herein, refers to an unbranched or branched saturated hydrocarbon chain. As used herein, alkyl has 1-20 carbons (*i.e.*, C_{1-20}alkyl), 1-16 carbons (*i.e.*, C_{1-16}alkyl), 1-12 carbons (*i.e.*, C_{1-12}alkyl), 1-10 carbons (*i.e.*, C_{1-10}alkyl), 1-8 carbons (*i.e.*, C_{1-8}alkyl), 1-6 carbons (*i.e.*, C_{1-6}alkyl), 1-4 carbons (*i.e.*, C_{1-4}alkyl), or 1-3 carbons (*i.e.*, C_{1-3}alkyl). Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, 2-pentyl, iso-pentyl, neo-pentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. When an alkyl residue having a specific number of carbons is named by chemical name or molecular formula, all positional isomers having that number of carbon atoms may be encompassed—for example, "butyl" includes n-butyl, sec-butyl, iso-butyl, and tert-butyl; and "propyl" includes n-propyl and iso-propyl. Certain commonly used alternative names may be used and will be understood by those of ordinary skill in the art. For instance, a divalent group, such as a divalent "alkyl" group, may be referred to as an "alkylene".

[0035] The term "alkoxy", as used herein, refers to an -O-alkyl moiety. Examples of alkoxy groups include, but are not limited to, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, and 1,2-dimethylbutoxy.

[0036] The term "aryl", as used herein, refers to a fully unsaturated carbocyclic ring moiety. The term "aryl" encompasses monocyclic and polycyclic fused-ring moieties. As used herein, aryl encompasses ring moieties comprising, for example, 6 to 20 annular carbon atoms (*i.e.*, C_{6-20}aryl), 6 to 16 annular carbon atoms (*i.e.*, C_{6-16}aryl), 6 to 12 annular carbon atoms (*i.e.*, C_{6-}

$_{12}$aryl), or 6 to 10 annular carbon atoms (*i.e.*, C_{6-10}aryl). Examples of aryl moieties include, but are not limited to, phenyl, naphthyl, fluorenyl, and anthryl.

[0037] The term "cycloalkyl", as used herein, refers to a saturated or partially unsaturated carbocyclic ring moiety. The term "cycloalkyl" encompasses monocyclic and polycyclic ring moieties, wherein the polycyclic moieties may be fused, branched, or spiro. Cycloalkyl includes cycloalkenyl groups, wherein the ring moiety comprises at least one annular double bond. Cycloalkyl includes any polycyclic carbocyclic ring moiety comprising at least one non-aromatic ring, regardless of the point of attachment to the remainder of the molecule. As used herein, cycloalkyl includes rings comprising, for example, 3 to 20 annular carbon atoms (*i.e.*, a C_{3-20}cycloalkyl), 3 to 16 annular carbon atoms (*i.e.*, a C_{3-16}cycloalkyl), 3 to 12 annular carbon atoms (*i.e.*, a C_{3-12}cycloalkyl), 3 to 10 annular carbon atoms (*i.e.*, a C_{3-10}cycloalkyl), 3 to 8 annular carbon atoms (*i.e.*, a C_{3-8}cycloalkyl), 3 to 6 annular carbon atoms (*i.e.*, a C_{3-6}cycloalkyl), or 3 to 5 annular carbon atoms (*i.e.*, a C_{3-5}cycloalkyl). Monocyclic cycloalkyl ring moieties include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic groups include, for example, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, adamantyl, norbomyl, decalinyl, 7,7-dimethyl -bicyclo [2.2.1]heptanyl, and the like. Still further, cycloalkyl also includes spiro cycloalkyl ring moieties, for example, spiro[2.5]octanyl, spiro[4.5]decanyl, or spiro [5.5]undecanyl.

[0038] The term "halo", as used herein, refers to atoms occupying group VIIA of The Periodic Table and includes fluorine (fluoro), chlorine (chloro), bromine (bromo), and iodine (iodo).

[0039] The term "heteroaryl", as used herein, refers to an aromatic (fully unsaturated) ring moiety that comprises one or more annular heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur. The term "heteroaryl" includes both monocyclic and polycyclic fused-ring moieties. As used herein, a heteroaryl comprises, for example, 5 to 20 annular atoms (*i.e.*, a 5-20 membered heteroaryl), 5 to 16 annular atoms (*i.e.*, a 5-16 membered heteroaryl), 5 to 12 annular atoms (*i.e.*, a 5-12 membered heteroaryl), 5 to 10 annular atoms (*i.e.*, a 5-10 membered heteroaryl), 5 to 8 annular atoms (*i.e.*, a 5-8 membered heteroaryl), or 5 to 6 annular atoms (*i.e.*, a 5-6 membered heteroaryl). Any monocyclic or polycyclic aromatic ring moiety comprising one or more annular heteroatoms is considered a heteroaryl, regardless of the point of attachment to the remainder of the molecule (*i.e.*, the heteroaryl moiety may be attached to the remainder of the molecule through any annular carbon or any annular heteroatom of the

heteroaryl moiety). Examples of heteroaryl groups include, but are not limited to, acridinyl, benzimidazolyl, benzindolyl, benzofuranyl, benzonaphthofuranyl, benzoxazolyl, benzotriazolyl, benzo[4,6]imidazo[l,2-a]pyridyl, carbazolyl, dibenzofuranyl, dibenzothiophenyl, furanyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, isoquinolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, phenazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, triazolyl, tetrazolyl, and triazinyl. Examples of the fused-heteroaryl rings include, but are not limited to, quinolinyl, isoquinolinyl, benzo[b]thiophenyl, indazolyl, benzo[d]imidazolyl, pyrazolo[1,5-a]pyridinyl, and imidazo[1,5-a]pyridinyl, wherein the heteroaryl can be bound *via* either ring of the fused system.

[0040] The term "heterocyclyl", as used herein, refers to a saturated or partially unsaturated cyclic moiety that encompasses one or more annular heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur. The term "heterocyclyl" includes both monocyclic and polycyclic ring moieties, wherein the polycyclic ring moieties may be fused, bridged, or spiro. Any non-aromatic monocyclic or polycyclic ring moiety comprising at least one annular heteroatom is considered a heterocyclyl, regardless of the point of attachment to the remainder of the molecule (*i.e.*, the heterocyclyl moiety may be attached to the remainder of the molecule through any annular carbon or any annular heteroatom of the heterocyclyl moiety). Further, the term heterocyclyl is intended to encompass any polycyclic ring moiety comprising at least one annular heteroatom wherein the polycyclic ring moiety comprises at least one non-aromatic ring, regardless of the point of attachment to the remainder of the molecule. As used herein, a heterocyclyl comprises, for example, 3 to 20 annular atoms (*i.e.*, a 3-20 membered heterocyclyl), 3 to 16 annular atoms (*i.e.*, a 3-16 membered heterocyclyl), 3 to 12 annular atoms (*i.e.*, a 3-12 membered heterocyclyl), 3 to 10 annular atoms (*i.e.*, a 3-10 membered heterocyclyl), 3 to 8 annular atoms (*i.e.*, a 3-8 membered heterocyclyl), 3 to 6 annular atoms (*i.e.*, a 3-6 membered heterocyclyl), 3 to 5 annular atoms (*i.e.*, a 3-5 membered heterocyclyl), 5 to 8 annular atoms (*i.e.*, a 5-8 membered heterocyclyl), or 5 to 6 annular atoms (*i.e.*, a 5-6 membered heterocyclyl). Examples of heterocyclyl groups include, *e.g.*, azetidinyl, azepinyl, benzodioxolyl, benzo[b][l,4]dioxepinyl, 1,4-benzodioxanyl, benzopyranyl, benzodioxinyl, benzopyranonyl, benzofuranonyl, dioxolanyl, dihydropyranyl, hydropyranyl, thienyl[l,3]dithianyl, decahydroisoquinolyl, furanonyl, imidazolinyl, imidazolidinyl, indolinyl,

indolizinyl, isoindolinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, oxiranyl, oxetanyl, phenothiazinyl, phenoxazinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, tetrahydropyranyl, trithianyl, tetrahydroquinolinyl, thiophenyl (*i.e.*, thienyl), thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. Examples of spiro heterocyclyl rings include, but are not limited to, bicyclic and tricyclic ring systems, such as oxabicyclo[2.2.2]octanyl, 2-oxa-7-azaspiro[3.5]nonanyl, 2-oxa-6-azaspiro[3.4]octanyl, and 6-oxa-1-azaspiro[3.3]heptanyl. Examples of fused heterocyclyl rings include, but are not limited to, 1,2,3,4-tetrahydroisoquinolinyl, 4,5,6,7-tetrahydrothieno[2,3-c]pyridinyl, indolinyl, and isoindolinyl, where the heterocyclyl can be bound via either ring of the fused system.

[0041] The terms "optional" and "optionally", as used herein, mean that the subsequently described event or circumstance may or may not occur and that the description includes instances where the event or circumstance occurs and instances where it does not. Accordingly, the term "optionally substituted" infers that any one or more (*e.g.*, 1, 2, 1 to 5, 1 to 3, 1 to 2, etc.) hydrogen atoms on the designated atom or moiety or group may be replaced or not replaced by an atom or moiety or group other than hydrogen. By way of illustration and not limitation, the phrase "methyl optionally substituted with one or more chloro" encompasses $-CH_3$, $-CH_2Cl$, $-CHCl_2$, and $-CCl_3$ moieties.

[0042] It is understood that aspects and embodiments described herein as "comprising" include "consisting of" and "consisting essentially of" embodiments.

[0043] The term "pharmaceutically acceptable salt", as used herein, of a given compound refers to salts that retain the biological effectiveness and properties of the given compound and which are not biologically or otherwise undesirable. "Pharmaceutically acceptable salts" include, for example, salts with inorganic acids, and salts with an organic acid. In addition, if the compounds described herein are obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Such compositions are well known in the pharmaceutical art. *See*, *e.g.*, *Handbook of Pharmaceutical Salts Properties, Selection, and Use*, International Union of Pure and Applied Chemistry, John

Wiley & Sons (2008), which is incorporated herein by reference. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare nontoxic pharmaceutically acceptable addition salts. Pharmaceutically acceptable acid addition salts may be prepared from inorganic or organic acids. Salts derived from inorganic acids include, *e.g.*, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Salts derived from organic acids include, *e.g.*, acetic acid, propionic acid, gluconic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid, salicylic acid, trifluoroacetic acid, and the like. Likewise, pharmaceutically acceptable base addition salts can be prepared from inorganic or organic bases. Salts derived from inorganic bases include, by way of example only, sodium, potassium, lithium, aluminum, ammonium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines. Specific examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(iso-propyl), amine, tri(n-propyl) amine, ethanolamine, 2-dimethylaminoethanol, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like.

[0044] Isotopically labeled forms of the compounds depicted herein may be prepared. Isotopically labeled compounds have structures depicted herein, except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. In some embodiments, a compound of formula (I), or formula (I') is provided wherein one or more hydrogen is replaced by deuterium or tritium.

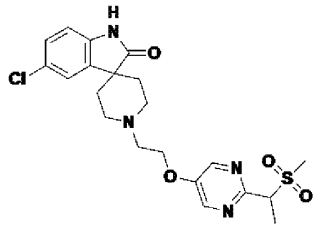
[0045] Some of the compounds provided herein may exist as tautomers. Tautomers are in equilibrium with one another. By way of illustration, amide containing compounds may exist in equilibrium with imidic acid tautomers. Regardless of which tautomer is shown and regardless of the nature of the equilibrium among tautomers, the compounds of this disclosure are understood by one of ordinary skill in the art to comprise both amide and imidic acid tautomers. Thus, for example, amide-containing compounds are understood to include their imidic acid tautomers. Likewise, imidic-acid containing compounds are understood to include their amide tautomers.

[0046] Also provided herein are prodrugs of the compounds depicted herein, or a pharmaceutically acceptable salt thereof. Prodrugs are compounds that may be administered to an individual and release, *in vivo*, a compound depicted herein as the parent drug compound. It is understood that prodrugs may be prepared by modifying a functional group on a parent drug compound in such a way that the modification is cleaved *in vivo* to release the parent drug compound. The development of prodrug compounds is well known in the pharmaceutical art. *See*, *e.g.*, Rautio, J., Kumpulainen, H., Heimbach, T. et al. Prodrugs: design and clinical applications. *Nat. Rev. Drug. Discov.* 7, 255–270 (2008), which is incorporated herein by reference.

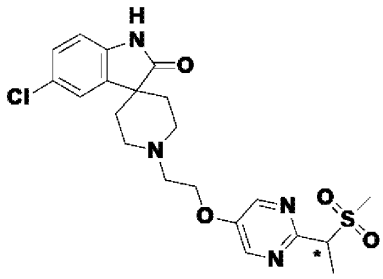
[0047] The compounds of the present disclosure, or their pharmaceutically acceptable salts, may include an asymmetric center and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- (or as (D)- or (L)- for amino acids). The present disclosure is meant to include all such possible isomers, as well as their racemic and optically pure forms and mixtures thereof in any ratio. Optically active (+) and (-), (*R*)- and (*S*)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or may be resolved using conventional techniques, for example, chromatography and/or fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or the resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC) or chiral supercritical fluid chromatography (SFC). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, unless specified otherwise, it is intended that the present disclosure includes both E and Z geometric isomers. Likewise, cis- and trans- are used in their conventional sense to describe relative spatial relationships.

[0048] A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds, but having different three-dimensional structures, which are not interchangeable. The present disclosure contemplates various stereoisomers, or mixtures thereof, and includes "enantiomers," which refers to two stereoisomers whose structures are non-superimposable mirror images of one another. "Diastereomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror images of each other.

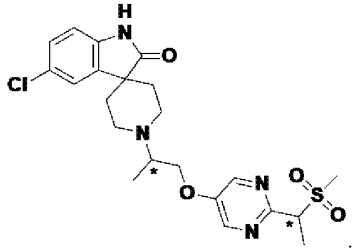
[0049] Where enantiomeric and/or diastereomeric forms exist of a given structure, flat bonds indicate that all stereoisomeric forms of the depicted structure may be present, *e.g.*,



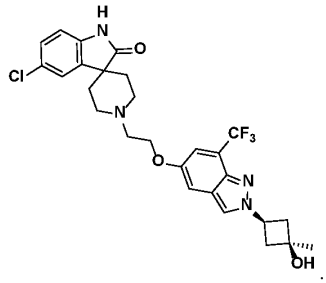
[0050] Where enantiomeric forms exist of a given structure, flat bonds and the presence of a " * " symbol indicate that the composition is made up of at least 90%, by weight, of a single isomer with unknown absolute stereochemistry, *e.g.*,



[0051] Where enantiomeric and/or diastereomeric forms exist of a given structure with two or more stereocenters, flat bonds and the presence of two or more " * " symbols indicate the composition is made up of at least 90%, by weight, of a single enantiomer or diastereomer with unknown absolute stereochemistry, *e.g.*,



[0052] Where enantiomeric and/or diastereomeric forms exist of a given structure, the composition is made up of at least 90%, by weight, dashes or wedges indicate a single enantiomer or diastereomer with known relative or absolute stereochemistry, *e.g*



[0053] Abbreviations used are those conventional in the art and are in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics,* 75th Ed, hereby incorporated herein by reference in its entirety. The following examples are intended to be illustrative only and not limiting in any way.

°C	degrees Celsius
µL	microliter
µW	microwave
$[M+XX]^+$	observed mass
AC_{50}	half-maximal activity concentration
Ac_2O	acetic anhydride
AIBN	azobisisobutyronitrile
app	apparent (NMR)
br	broad (NMR)
$BH_3 \cdot THF$	borane-tetrahydrofuran complex
BBr_3	boron tribromide
BnCl	benzyl chloride
$B(Pin)_2$	bis(pinacolato)diboron
Calc'd	calculated
Cbz-Cl	benzyl chloroformate
CCl_4	carbontetrachloride
CDI	carbonyldiimidazole
$CHCl_3$	chloroform
CO_2	carbon dioxide
Cs_2CO_3	cesium carbonate
CuI	copper iodide
d	deuterated (NMR solvents)
d	doublet (NMR)
dd	doublet of doublets (NMR)
DAST	diethylaminosulfur trifluoride
DMA	*N,N*-dimethylacetamide
DCE	1,2-dichloroethane
DCM	dichloromethane
DIAD	diisopropyl azodicarboxylate
DIEA	*N,N*-diisopropylethylamine
DME	dimethoxyethane
DMEDA	*N,N*-dimethylethylenediamine
DMA	dimethylacetamide
DMF	*N,N*-dimethylformamide
DPPF	1,1'-bis(diphenylphosphino)ferrocene
EC_{50}	half-maximal effective concentration
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et_3N	triethyl amine

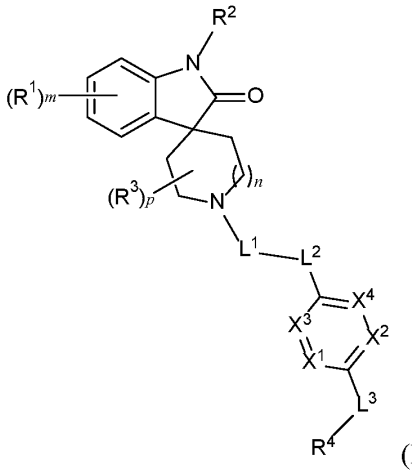
EtOAc	ethyl acetate
EtOH	ethanol
g	grams
h	hours
H	hydrogen
H_2	hydrogen gas
H_2O	water
H_2O_2	hydrogen peroxide
HATU	N-[(Dimethylamino)-1H-1,2,3-triazolo-[4,5-b]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide
HCl	hydrochloric acid
HOBt	hydroxybenzotriazole
HPLC	high-performance liquid chromatography
In vacuo	in a vacuum
$(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$	[4,4′-Bis(1,1-dimethylethyl)-2,2′-bipyridine-N1,N1′]bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-N]phenyl-C]Iridium(III) hexafluorophosphate
IUPAC	International Union of Pure and Applied Chemistry
J	J-coupling value (NMR)
K_2CO_3	potassium carbonate
KI	potassium iodide
KOAc	potassium acetate
KOH	potassium hydroxide
$LiAlH_4$	lithium aluminum hydride
LiHMDS	lithium bis(trimethylsilyl)amide
LiOH	lithium hydroxide
MeOH	methanol
MeCN	acetonitrile
MHz	megahertz
m	multiplet (NMR)
mg	milligrams
min	minutes
mL	milliliter
mmol	millimole
mM	millimolar

M	molarity or molar
m-CPBA	meta-chloroperoxybenzoic acid
MeCN	acetonitrile
$MeSO_2Na$	sodium methanesulfinate
MS	mass spectrometry
MsCl	methanesulfonyl chloride
Ms_2O	methanesulfonic anhydride
MTBE	methyl *tert*-butyl ether
n/a	not applicable
$NaBH(OAc)_3$	sodium triacetoxyborohydride
NaH	sodium hydride
NBS	*N*-bromosuccinimide
NH_4	ammonium
NH_4OH	ammonium hydroxide
NH_4HCO_3	ammonium bicarbonate
Na_2SO_4	sodium sulfate
$NaBH_3CN$	sodium cyanoborohydride
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
$NaIO_4$	sodium periodate
NaOH	sodium hydroxide
OsO_4	osmium tetraoxide
Pd/C	palladium on carbon
PCy_3	tricyclohexylphosphine

$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
$Pd(PPh_3)_2$	bis(triphenylphosphine)palladium(II) chloride
$Pd(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
pH	potential of hydrogen
PPh_3	triphenyl phosphine
PSI	pounds per square inch
s	singlet (NMR)
SEMCl	(2-chloromethoxyethyl)trimethylsilane
SFC	super fluid chromatography
$SOCl_2$	thionyl chloride
t	triplet (NMR)
T3P	propanephosphonic acid anhydride
TBAB	tetrabutylammonium bromide
TBAI	tetrabutylammonium iodide
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMSCl	trimethylsilyl chloride
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
$Zn(CN)_2$	zinc cyanide

COMPOUNDS

[0054] Provided herein is a compound of formula (II):



(II),

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

m is an integer from 0 to 4;

n is an integer from 0 to 2;

p is an integer from 0 to 10;

R^1, if present is, independently at each occurrence selected from the group consisting of halo, -CN, C_{1-6}alkoxy, and C_{1-6}alkyl, wherein

the C_{1-6}alkoxy of R^1 is optionally substituted with one or more halo, and

the C_{1-6}alkyl of R^1 is optionally substituted with one or more halo;

R^2 is H, C_{1-6}alkyl, C_{3-10}cycloalkyl, or 3-15 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^2 is optionally substituted with one or more deuterium, halo, -OH, $-NH_2$, or C_{1-6}alkoxy, and

the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more -OH;

R^3, if present, is C_{1-6}alkyl;

L^1 is C_{1-6}alkylene, wherein

the C_{1-6}alkylene of L^1 is optionally substituted with one or more deuterium or C_{1-6}alkyl, and wherein

the C_{1-6}alkyl is further optionally substituted with one or more -OH or C_{1-6}alkoxy;

L^2 is O or N(R^x), wherein R^x is H or C_{1-6}alkyl; and

either

(1) L^3 is absent or is O, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or C_{1-6}alkylene, wherein

the C_{3-10}cycloalkyl of L^3 is optionally substituted with one or more -OH or C_{1-6}alkyl,

the C_{1-6}alkylene of L^3 is optionally substituted with one or more -OH or C_{1-6}alkyl, wherein

the C_{1-6}alkyl is optionally substituted with one or more -OH, and

the 3-10 membered heterocyclyl of L^3 is optionally substituted with one or more –OH or C_{1-6}alkyl;

X^1 and X^2 are each independently N or $C(R^5)$; and

R^4 is:

(i) $-S(O)_2-R^a$;

(ii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^4 is optionally substituted with one or more C_{1-6}alkyl;

(iii) $-N(R^d)_2$, wherein R^d is independently at each occurrence H, C_{1-6} alkyl, or $-S(O)_2-R^a$, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more -OH,

(iv) $-NS(O)-(C_{1-6}alkyl)_2$, wherein the C_{1-6}alkyl is optionally substituted with one or more –OH,

(v) $-C(O)-N(R^e)_2$ wherein R^e is independently at each occurrence H, C_{1-6} alkyl, or 3-10 membered heterocycle, wherein

the 3-10 membered heterocycle of R^e is optionally substituted with one or more oxo, or both R^e together with the N to which they are attached are taken together to form a 3-10 membered heterocyclyl, wherein

the 3-10 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, $-NH-S(O)_2-R^a$, or $-S(O)_2-R^a$,

(vi) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl, -OH , oxo or $-S(O)_2R^a$,

(vii) $-S(O)-N(C_{1-6}alkyl)-(C_{1-6}alkyl)$,

(viii) -CN,

(ix) $-(CH_2)_qOH$, wherein q is an integer from 0-6,

(x) $-C(O)-C_{1-6}$alkyl, or

(xi) $-P(O)(C_{1-6}alkyl)_2$;

or

(2) L^3 is absent; and

one of X^1 and X^2 is N or C(R^5); and

the other of X^1 and X^2 is N or C that is taken together with R^4, and the atoms to which they are attached, to form a 5-10 membered heterocyclyl or a 5-20 membered heteroaryl, wherein

the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein

R^b is, independently at each occurrence, selected from the group consisting of -OH, halo, oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -$S(O)_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, OH, -$S(O)_2$-C_{1-6}alkyl, or C_{3-10}cycloalkyl, and wherein

the C_{3-10}cycloalkyl of the C_{1-6}alkyl of R^b is further optionally substituted with one or more C_{1-6}alkyl or -OH and

the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more -OH, C_{3-10}cycloalkyl, or C_{1-6}alkyl, and wherein

the C_{1-6}alkyl of the C_{3-10}cycloalkyl of R^b is further optionally substituted with one or more -OH, deuterium, or halo, and

the 5-20 membered heteroaryl is optionally substituted with one or more R^c, wherein

R^c is, independently at each occurrence, selected from the group consisting of halo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -$S(O)_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more -$S(O)_2$-C_{1-6}alkyl,

the C_{3-10}cycloalkyl of R^c is optionally substituted with one or more -OH or C_{1-6}alkyl, and

the 3-10 membered heterocyclyl of R^c is optionally substituted with one or more -OH or C_{1-6}alkyl, and wherein

the C_{1-6}alkyl of the 3-10 membered heterocyclyl of R^c is further optionally substituted with one or more -OH;

R^a is, independently at each occurrence:

(i) C_{1-6}alkyl optionally substituted with one or more halo, -OH, -$S(O)_2$-C_{1-6}alkyl, or -N(C_{1-6}alkyl)-C(O)-C_{1-6}alkyl,

(ii) C_{3-10}cycloalkyl optionally substituted with one or more -OH, -C(O)$_2$-C_{1-6}alkyl, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, or –C(O)-C_{3-10}heterocyclyl, or C_{1-6}alkyl, wherein

the C_{1-6}alkyl is optionally substituted with one or more -OH,

(iii) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl, or

(iv) NH(C_{1-6}alkyl);

R^5 is, independently at each occurrence, H, halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein

the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo or -OH, and

the C_{1-6}alkoxy of R^5 is optionally substituted with one or more halo;

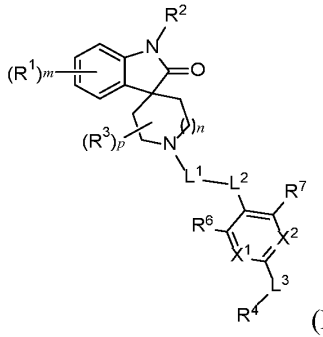
X^3 is N or C(R^6);

X^4 is N or C(R^7);

and

R^6 and R^7 are each independently H or halo.

[0055] 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:

m is an integer from 0 to 4;

n is an integer from 0 to 2;

p is an integer from 0 to 10;

R^1, if present is, independently at each occurrence selected from the group consisting of halo, -CN, C_{1-6}alkoxy, or C_{1-6}alkyl, wherein

the C_{1-6}alkoxy of R^1 is optionally substituted with one or more halo, and

the C_{1-6}alkyl of R^1 is optionally substituted with one or more halo;

R^2 is H, C_{1-6}alkyl, C_{3-10}cycloalkyl, or 3-15 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^2 is optionally substituted with one or more halo, -OH, $-NH_2$, or C_{1-6}alkoxy, and

the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more -OH;

R^3, if present, is C_{1-6}alkyl;

L^1 is C_{1-6}alkylene, wherein the C_{1-6}alkylene of L^1 is optionally substituted with one or more C_{1-6}alkyl, and wherein the C_{1-6}alkyl is further optionally substituted with one or more -OH or C_{1-6}alkoxy;

L^2 is O or $N(R^x)$, wherein R^x is H or C_{1-6}alkyl; and

either

(1) L^3 is absent or is O, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or C_{1-6}alkylene, wherein

the C_{3-10}cycloalkyl is optionally substituted with one or more –OH or C_{1-6}alkyl,

the C_{1-6}alkylene of L^3 is optionally substituted with one or more –OH or C_{1-6}alkyl, and

the 3-10 membered heterocyclyl is optionally substituted with one or more –OH;

X^1 and X^2 are each independently N or $C(R^5)$; and

R^4 is:

(i) $-S(O)_2-R^a$;

(ii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^4 is optionally substituted with one or more C_{1-6}alkyl;

(iii) $-N(R^d)_2$, wherein R^d is independently at each occurrence H, C_{1-6} alkyl, or $-S(O)_2-R^a$, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more –OH,

(iv) $-NS(O)-(C_{1-6}alkyl)_2$, wherein the C_{1-6}alkyl is optionally substituted with one or more –OH,

(v) $-C(O)-N(R^e)_2$ wherein R^e is independently at each occurrence H, C_{1-6} alkyl, or 3-10 membered heterocycle, wherein the 3-10 membered heterocycle is optionally substituted with one or more oxo, or both R^e together with the N to which they are attached are taken together to form a 3-10 membered heterocyclyl, wherein the 3-10 membered

heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, -NH-$S(O)_2$-R^a, or -$S(O)_2$-R^a,

(vi) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl, -OH, oxo or -$S(O)_2R^a$,

(vii) -S(O)-N(C_{1-6}alkyl)-(C_{1-6}alkyl),

(viii) -CN,

(ix) -$(CH_2)_q$OH, wherein q is an integer from 0-6,

(x) -C(O)-C_{1-6}alkyl, or

(xi) -P(O)(C_{1-6}alkyl)$_2$;

or

(2) L^3 is absent; and

one of X^1 and X^2 is N or C(R^5); and

the other of X^1 and X^2 is N or C that is taken together with R^4 and the atoms to which they are attached to form a 5-10 membered heterocyclyl or a 5-20 membered heteroaryl, wherein

the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is, independently at each occurrence, selected from the group consisting of halo, oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -$S(O)_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, OH, -$S(O)_2$-C_{1-6}alkyl, or C_{3-10}cycloalkyl, and

wherein the C_{3-10}cycloalkyl of the C_{1-6}alkyl of R^b is further optionally substituted with one or more C_{1-6}alkyl or -OH and

the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more -OH, C_{3-10}cycloalkyl, or C_{1-6}alkyl, and

wherein the C_{1-6}alkyl of the C_{3-10}cycloalkyl of R^b is further optionally substituted with one or more –OH, and

the 5-20 membered heteroaryl is optionally substituted with one or more R^c, wherein R^c is, independently at each occurrence, selected from the group consisting of halo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -$S(O)_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more -$S(O)_2$-C_{1-6}alkyl,

the C_{3-10}cycloalkyl of R^c is optionally substituted with one or more –OH or C_{1-6}alkyl,

and the 3-10 membered heterocyclyl of R^c is optionally substituted with one or more -OH or C_{1-6}alkyl, and

wherein the C_{1-6}alkyl of the 3-10 membered heterocyclyl of R^c is further optionally substituted with one or more -OH;

R^a is, independently at each occurrence:

(i) C_{1-6}alkyl optionally substituted with one or more halo, -OH, -$S(O)_2$-C_{1-6}alkyl, or -N(C_{1-6}alkyl)-C(O)-C_{1-6}alkyl,

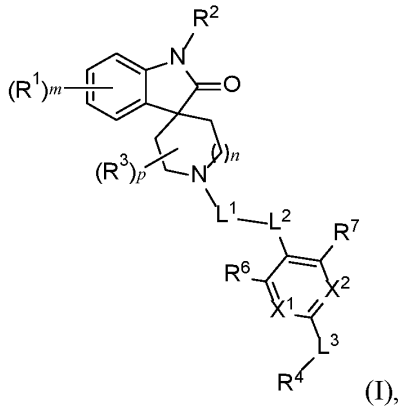
(ii) C_{3-10}cycloalkyl optionally substituted with one or more -OH, -$C(O)_2$-C_{1-6}alkyl, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, or –C(O)-C_{3-10}heterocyclyl, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more -OH, or

(iii) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl;

R^5 is, independently at each occurrence, H, halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH and wherein the C_{1-6}alkoxy of R^5 is optionally substituted with one or more halo; and

R^6 and R^7 are each independently H or halo.

[0056] 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:

m is an integer from 0 to 4;

n is an integer from 0 to 2;

p is an integer from 0 to 10;

R^1, if present is, independently at each occurrence selected from the group consisting of halo, -CN, C_{1-6}alkoxy or -C_{1-6}alkyl, wherein

the C_{1-6}alkoxy of R^1 is optionally substituted with one or more halo, and

the C_{1-6}alkyl of R^1 is optionally substituted with one or more halo;

R^2 is H, C_{1-6}alkyl, C_{3-10}cycloalkyl, or 3-15 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^2 is optionally substituted with one or more halo, -OH, -NH_2, or C_{1-6}alkoxy, and

the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more -OH;

R^3, if present, is C_{1-6}alkyl;

L^1 is C_{1-6}alkylene, wherein the C_{1-6}alkylene of L^1 is optionally substituted with one or more C_{1-6}alkyl, and wherein the C_{1-6}alkyl is further optionally substituted with one or more -OH or C_{1-6}alkoxy;

L^2 is O or N(R^x), wherein R^x is H or C_{1-6}alkyl; and

either

(1) L^3 is absent or is O, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or C_{1-6}alkylene, wherein

the C_{1-6}alkylene of L^3 is optionally substituted with one or more C_{1-6}alkyl, and

the 3-10 membered heterocyclyl is optionally substituted with one or more –OH;

X^1 and X^2 are each independently N or C(R^5); and

R^4 is:

(i) -$S(O)_2$-R^a,

(ii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^4 is optionally substituted with one or more C_{1-6}alkyl,

(iii) -N(R^d)$_2$, wherein R^d is independently at each occurrence H, C_{1-6} alkyl, or -$S(O)_2$-R^a, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more –OH,

(iv) -NS(O)-(C_{1-6}alkyl)$_2$, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more –OH,

(v) -C(O)-N(R^e)$_2$ wherein R^e is independently at each occurrence H, C_{1-6} alkyl, or 3-10 membered heterocycle, wherein the 3-10 membered heterocycle is optionally substituted with one or more oxo, or both R^e together with the N to which they are attached are taken together to form a 3-10 membered heterocyclyl, wherein the 3-10 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, NH-S(O)$_2$-R^a, or -S(O)$_2$-R^a,

(vi) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl or oxo,

(vii) -S(O)-N(C_{1-6}alkyl)-(C_{1-6}alkyl), or

(viii) –CN;

or

(2) L^3 is absent; and

one of X^1 and X^2 is N or C(R^5); and

the other of X^1 and X^2 is N or C that is taken together with R^4 and the atoms to which they are attached to form a 5-10 membered heterocyclyl or a 5-20 membered heteroaryl, wherein

the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is, independently at each occurrence, selected from the group consisting of halo, oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -S(O)$_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, OH, or -S(O)$_2$-C_{1-6}alkyl, and

the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more -OH, and

the 5-20 membered heteroaryl is optionally substituted with one or more R^c, wherein R^c is, independently at each occurrence, selected from the group consisting of halo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -S(O)$_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more -S(O)$_2$-C_{1-6}alkyl, and

the C_{3-10}cycloalkyl of R^c is optionally substituted with one or more -OH;

R^a is, independently at each occurrence:

(i) C_{1-6}alkyl optionally substituted with one or more halo, -OH, -$S(O)_2$-C_{1-6}alkyl, or -N(C_{1-6}alkyl)-C(O)-C_{1-6}alkyl, or

(ii) C_{3-10}cycloalkyl optionally substituted with one or more -OH, -$C(O)_2$-C_{1-6}alkyl, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, or –C(O)-C_{3-10}heterocyclyl, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more -OH, or

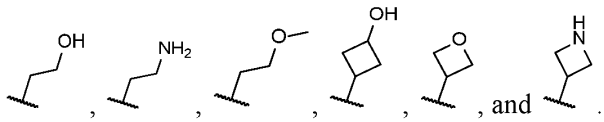
(iii) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl;

R^5 is, independently at each occurrence, H, halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH and wherein the C_{1-6}alkoxy is optionally substituted with one or more halo; and

R^6 and R^7 are each independently H or halo.

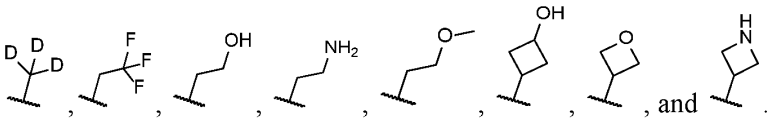
[0057] Any embodiments provided herein of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof, are also embodiments of a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0058] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, *n* is an integer from 0 to 2. In some embodiments, *n* is 0. In some embodiments, *n* is 1. In some embodiments, *n* is 2. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof. In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is H, C_{1-6}alkyl, C_{3-10}cycloalkyl, or 3-15 membered heterocyclyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more halo, -OH, -NH_2, or C_{1-6}alkoxy, and the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more -OH. In some embodiments, R^2 is H, C_{1-3}alkyl, C_{3-6}cycloalkyl, or 3-6 membered heterocyclyl, wherein the C_{1-3}alkyl of R^2 is optionally substituted with one or more halo, -OH, -NH_2, or C_{1-3}alkoxy, and the C_{3-6}cycloalkyl of R^2 is optionally substituted with one or more -OH. In some embodiments, R^2 is selected from the group consisting of H,  ,



. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0060] In some embodiments of a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is H, C_{1-6}alkyl, C_{3-10}cycloalkyl, or 3-15 membered heterocyclyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more deuterieum, halo, -OH, $-NH_2$, or C_{1-6}alkoxy, and the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more -OH. In some embodiments, R^2 is H, C_{1-3}alkyl, C_{3-6}cycloalkyl, or 3-6 membered heterocyclyl, wherein the C_{1-3}alkyl of R^2 is optionally substituted with one or more deuterieum, halo, -OH, $-NH_2$, or C_{1-3}alkoxy, and the C_{3-6}cycloalkyl of R^2 is optionally substituted with one or more -OH. In some embodiments, R^2 is selected from the group consisting of

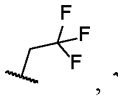
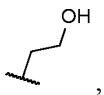


.

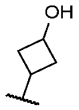
[0061] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is H. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0062] In some embodiments of a compound of formula (I), formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl. In some embodiments, R^2 is C_{1-3}alkyl. In some embodients R^2 is methyl or ethyl. In some embodiments, R^2 is methyl. In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0063] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl optionally substituted with one or more halo, -OH, $-NH_2$, or C_{1-6}alkoxy. In some embodiments, R^2 is C_{1-3}alkyl

optionally substituted with one or more halo, -OH, -NH_2, or C_{1-3}alkoxy. In some embodiments, R^2 is methyl. In some embodiments, R^2 is ethyl optionally substituted with one or more halo, -OH, -NH_2, or C_{1-6}alkoxy. In some embodiments, R^2 is selected from the group consisting of  ,  ,  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0064] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl optionally substituted with one or more deuterium, halo, -OH, -NH_2, or C_{1-6}alkoxy. In some embodiments, R^2 is C_{1-3}alkyl optionally substituted with one or more deuterium, halo, -OH, -NH_2, or C_{1-3}alkoxy. In some embodiments, R^2 is methyl. In some embodiments, R^2 is ethyl optionally substituted with one or more halo, -OH, -NH_2, or C_{1-6}alkoxy. In some embodiments, R^2 is selected from the group consisting of  ,  ,  ,  , and  .

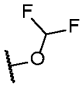
[0065] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more -OH. In some embodiments, R^2 is C_{3-6}cycloalkyl, wherein the C_{3-6}cycloalkyl of R^2 is optionally substituted with one or more -OH. In some embodiments, R^2 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0066] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is 3-15 membered heterocyclyl. In some embodiments, R^2 is 3-6 membered heterocyclyl. In some embodiments, R^2 is

 , and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0067] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, *m* is an integer from 0 to 4. In some embodiments, *m* is an integer from 0 to 2. In some embodiments, *m* is 0. In some embodiments *m* is 1. In some embodiments, *m* is 2. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0068] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is halo, -CN, C_{1-6}alkoxy or -C_{1-6}alkyl, wherein the C_{1-6}alkoxy or R^1 is optionally substituted with one or more halo, and wherein the C_{1-6}alkyl of R^1 is optionally substituted with one or more halo. In some embodiments, R^1 is halo, -CN, C_{1-3}alkoxy, or -C_{1-3}alkyl, wherein the C_{1-3}alkoxy of R^1 is optionally substituted with one or more halo, and wherein the C_{1-3}alkyl of R^1 is optionally substituted with one or more halo. In some embodiments, R^1 is selected from the group consisting of Cl, Br, -CN, methyl,  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0069] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is halo, -CN, C_{1-6}alkoxy or -C_{1-6}alkyl, wherein the C_{1-6}alkoxy or R^1 is optionally substituted with one or more halo, and wherein the C_{1-6}alkyl of R^1 is optionally substituted with one or more halo. In some embodiments, R^1 is halo, -CN, C_{1-3}alkoxy, or -C_{1-3}alkyl, wherein the C_{1-3}alkoxy of R^1 is optionally substituted with one or more halo, and wherein the C_{1-3}alkyl of R^1 is optionally substituted with one or more halo. In some embodiments, R^1 is selected from the group consisting of Cl, Br, F, I, -CN, methyl,  , and

 . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0070] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is halo. In some embodiments R^1 is Cl. In some embodiments, R^1 is Br. In some embodiments, R^1 is F. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0071] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is halo. In some embodiments R^1 is Cl. In some embodiments, R^1 is Br. In some embodiments, R^1 is F. In some embodiments R^1 is I. In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0072] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is $C_{1\text{-}6}$alkyl, wherein the $C_{1\text{-}6}$alkyl of R^1 is optionally substituted with one or more halo. In some embodiments, R^1 is $C_{1\text{-}3}$alkyl, wherein the $C_{1\text{-}3}$alkyl of R^1 is optionally substituted with one or more halo. In some embodiments, R^1 is $C_{1\text{-}3}$alkyl, wherein the $C_{1\text{-}3}$alkyl of R^1 is optionally substituted with one or more F. In some embodiments, R^1 is methyl, wherein the methyl of R^1 is optionally substituted with one or more F. In some embodiments, R^1 is methyl. In some embodiments, R^1 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0073] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is -CN. In some variations, theembodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer

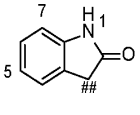
or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

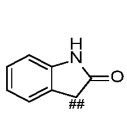
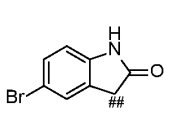
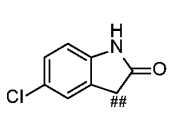
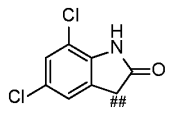
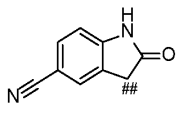
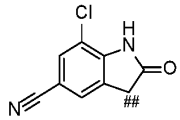
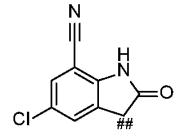
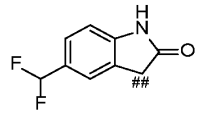
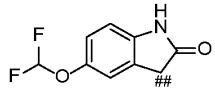
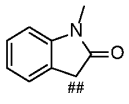
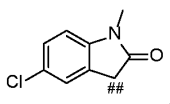
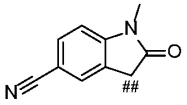
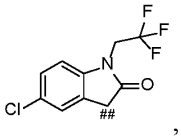
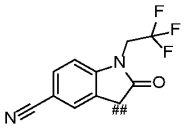
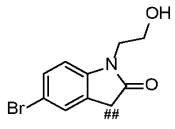
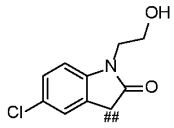
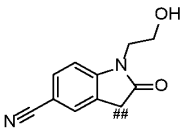
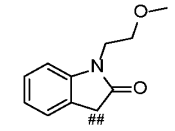
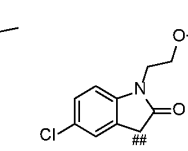
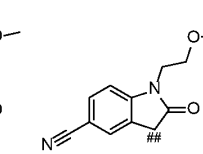
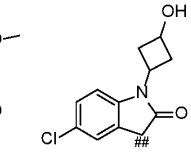
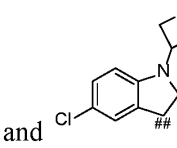
[0074] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is C_{1-6}alkoxy, wherein the C_{1-6}alkoxy of R^1 is optionally substituted with one or more halo. In some embodiments, R^1 is C_{1-3}alkoxy, wherein the C_{1-3}alkoxy of R^1 is optionally substituted with one or more halo. In some embodiments, R^1 is C_{1-3}alkoxy, wherein the C_{1-3}alkoxy of R^1 is optionally substituted with one or more F. In some embodiments, R^1 is methoxy, wherein the methoxy of R^1 is optionally substituted with one or more F. In some embodiments, R^1 is  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0075] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, p is an integer from 0 to 10. In some embodiments, p is 0 or 1. In some embodiments, p is 0. In some embodiments, p is 1. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

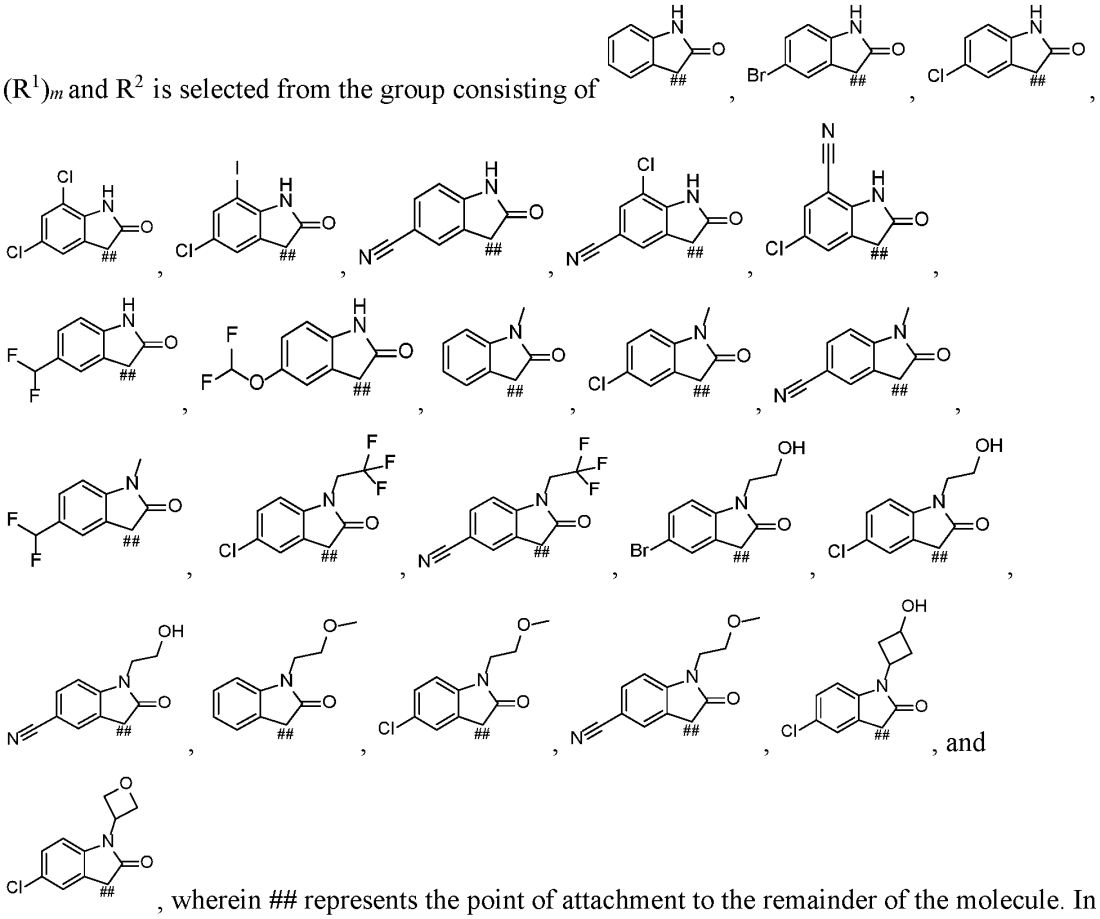
[0076] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^3 is C_{1-6}alkyl. In some embodiments, R^3 is C_{1-3}alkyl. In some embodiments, R^3 is methyl. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0077] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, the ring bearing $(R^1)_m$ and R^2 is a 2-indolinone optionally substituted at one or more of positions 1, 5, and 7. In some embodiments, the 2-indolinone ring is unsubstituted. In some embodiments, the 2-indolinone ring is substituted at position 1. In some embodiments, the 2-indolinone ring is substituted at position 5. In

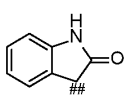
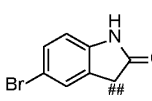
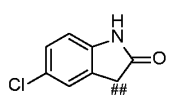
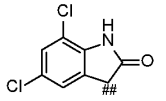
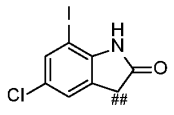
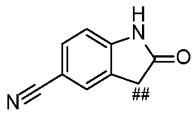
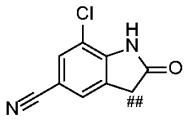
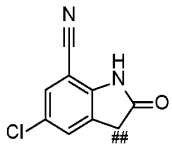
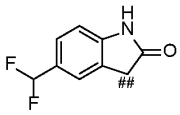
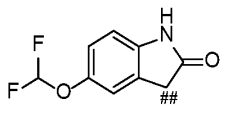
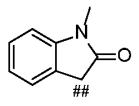
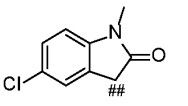
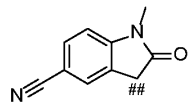
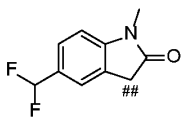
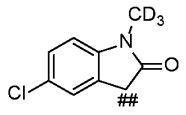
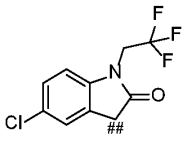
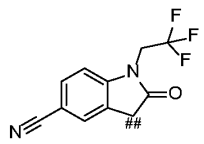
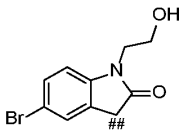
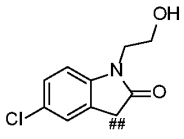
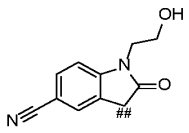
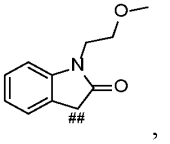
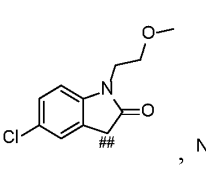
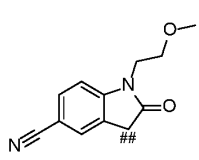
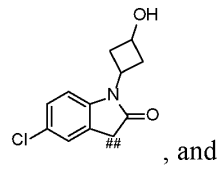
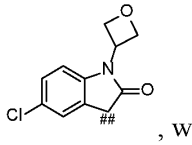
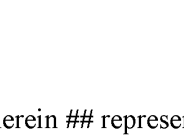
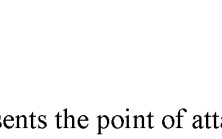
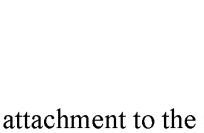
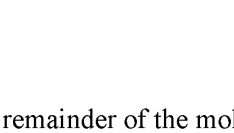
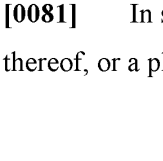
some embodiments, the 2-indolinone ring is substituted at position 7. In some embodiments, the 2-indolinone ring is substituted at positions 1, and 5. In some embodiments, the 2-indolinone ring is substituted at positions 5 and 7. In some embodiments, the 2-indolinone ring is substituted at positions 1, 5, and 7. In some embodiments positions 1, 5 and 7 are defined as indicated in the structure,  , wherein position 1 is a N atom, each of positions 5 and 7 is a C atom, and ## represent the point of attachment to the remainder of the molecule. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

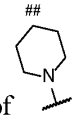
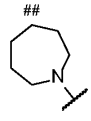
[0078] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, the ring bearing $(R^1)_m$ and R^2 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  , wherein ## represents the point of attachment to the remainder of the molecule. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or

(II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

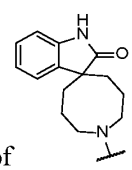
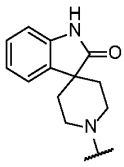
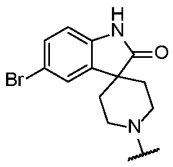
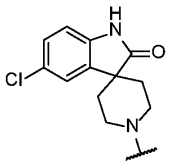
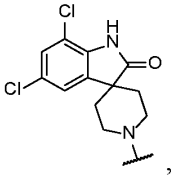
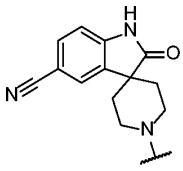
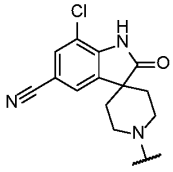
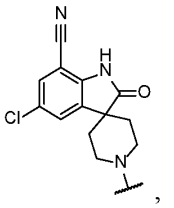
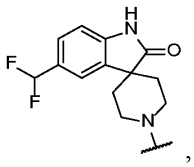
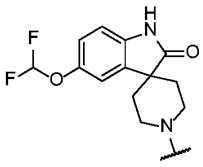
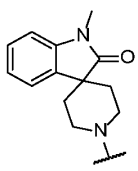
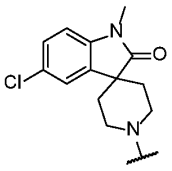
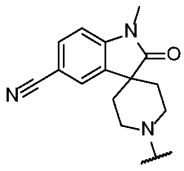
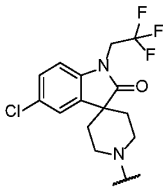
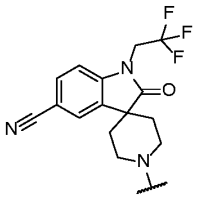
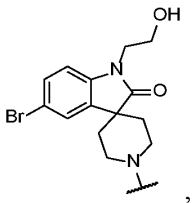
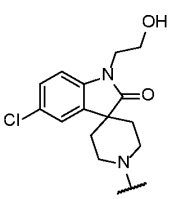
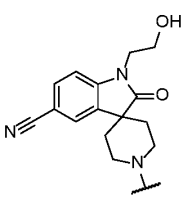
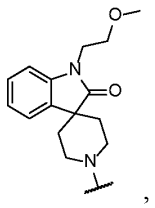
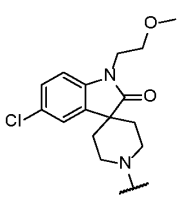
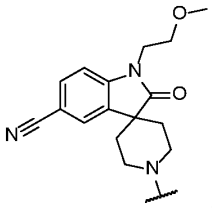
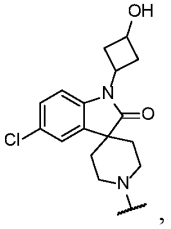
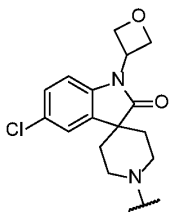
[0079] In some embodiments of a compound of formula (I), formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, the ring bearing $(R^1)_m$ and R^2 is selected from the group consisting of  , wherein ## represents the point of attachment to the remainder of the molecule. In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0080] In some embodiments of a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, the ring bearing $(R^1)_m$ and R^2

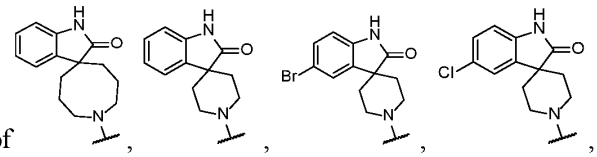
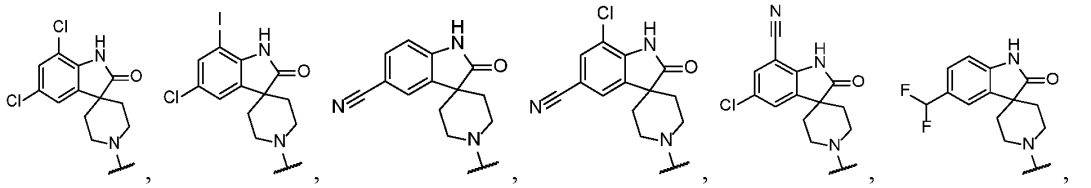
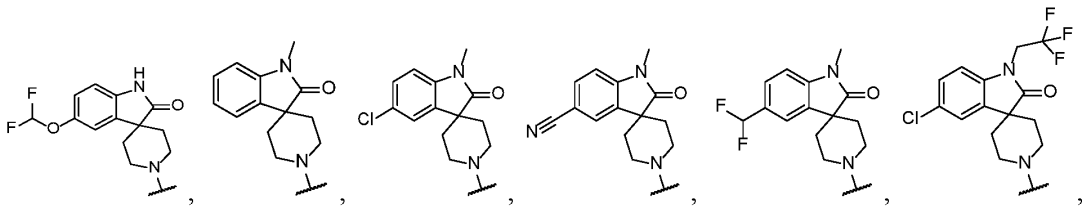
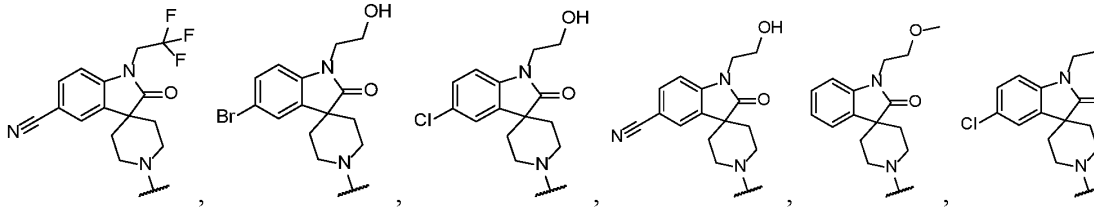
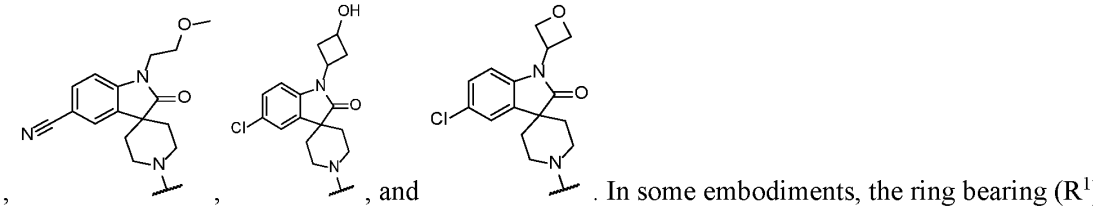
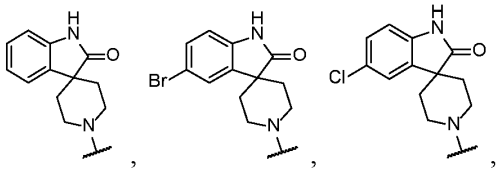
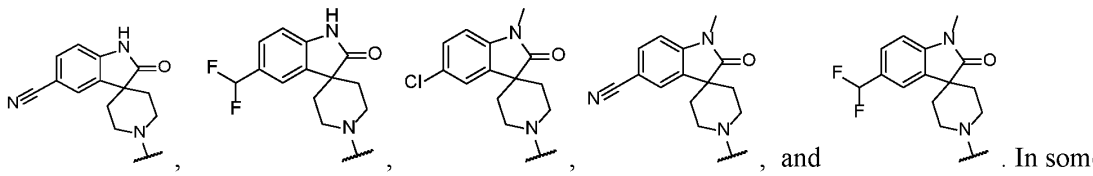
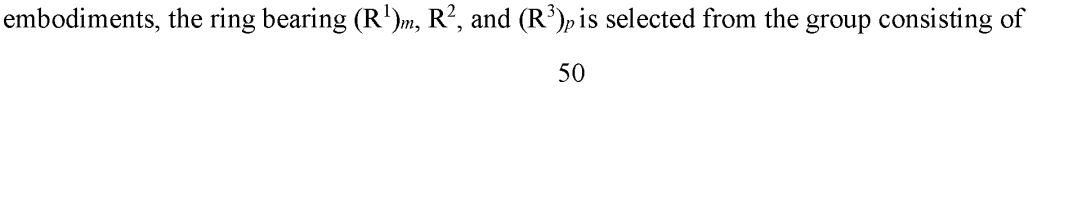
is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  , wherein ## represents the point of attachment to the remainder of the molecule.

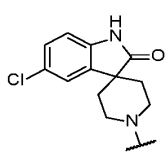
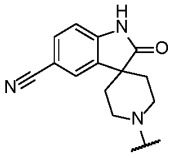
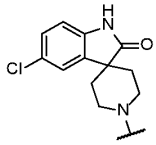
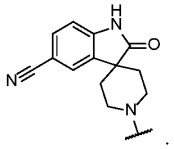
[0081] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, the ring bearing $(R^3)_p$ is selected from the group consisting of  , and,  , wherein ## represents the point of attachment to the remainder of the molecule. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

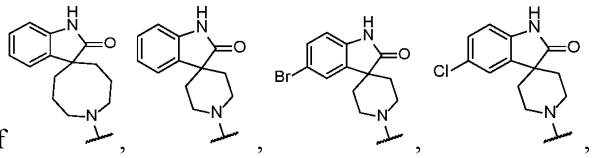
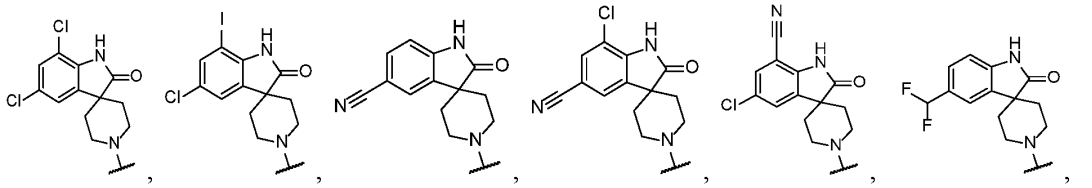
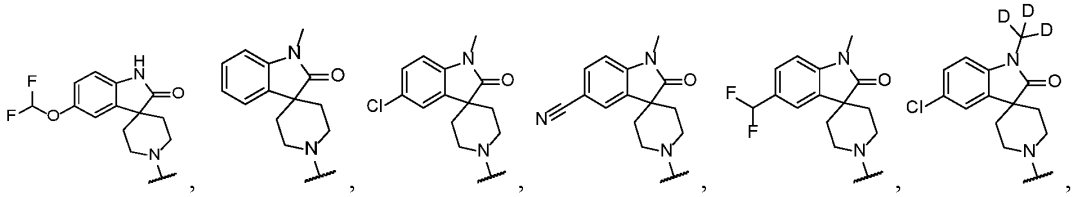
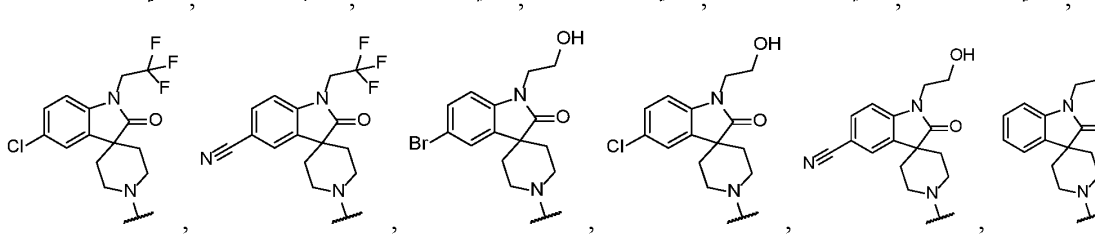
[0082] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, the ring bearing $(R^1)_m$, R^2, and

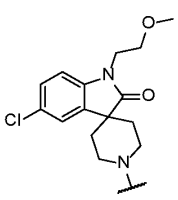
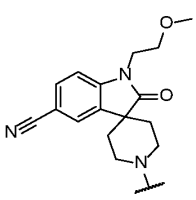
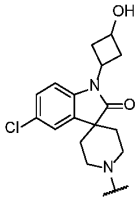
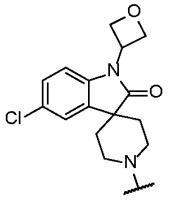
$(R^3)_p$ is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

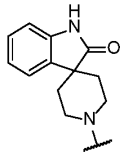
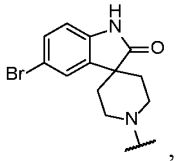
[0083] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, the ring bearing $(R^1)_m$, R^2, and

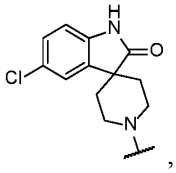
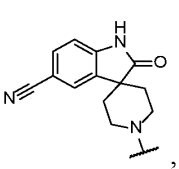
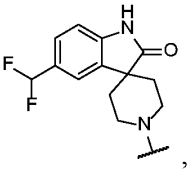
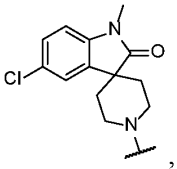
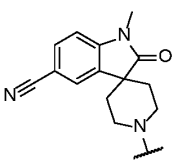
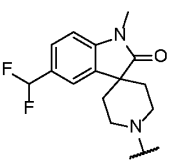
$(R^3)_p$ is selected from the group consisting of  ,  ,  ,  ,  , , and . In some embodiments, the ring bearing $(R^1)_m$, R^2, and $(R^3)_p$ is selected from the group consisting of  ,  , and  . In some embodiments, the ring bearing $(R^1)_m$, R^2, and $(R^3)_p$ is selected from the group consisting of

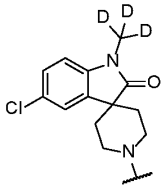
 and  . In some embodiments, the ring bearing $(R^1)_m$, R^2, and $(R^3)_p$ is  . In some embodiments, the ring bearing $(R^1)_m$, R^2, and $(R^3)_p$ is  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

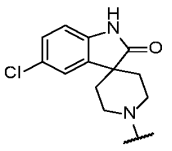
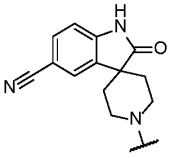
[0084] In some embodiments of a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, the ring bearing $(R^1)_m$, R^2, and $(R^3)_p$ is selected from the group consisting of  ,  ,  ,  , .

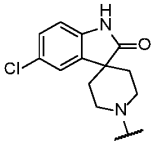




, , , , and . In some embodiments, the

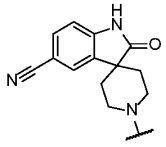


ring bearing $(R^1)_m$, R^2, and $(R^3)_p$ is selected from the group consisting of , ,

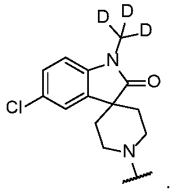






, , , , , ,


and . In some embodiments, the ring bearing $(R^1)_m$, R^2, and $(R^3)_p$ is selected from the

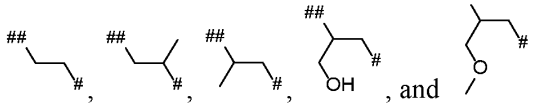
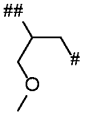


group consisting of and . In some embodiments, the ring bearing

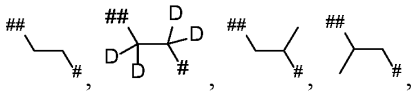
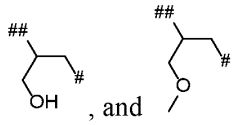

$(R^1)_m$, R^2, and $(R^3)_p$ is . In some embodiments, the ring bearing $(R^1)_m$, R^2, and $(R^3)_p$ is


. In some embodiments, the ring bearing $(R^1)_m$, R^2, and $(R^3)_p$ is


.

[0085] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1 is C_{1-6}alkylene optionally

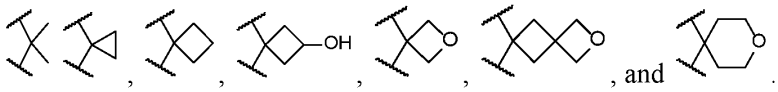
substituted with one or more C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with -OH or C_{1-6}alkoxy. In some embodiments, L^1 is C_{1-3}alkylene optionally substituted with one or more C_{1-3}alkyl, wherein the C_{1-3}alkyl is optionally substituted with -OH or C_{1-3}alkoxy. In some embodiments, L^1 is methylene. In some embodiments, L^1 is ethylene. In some embodiments, L^1 is ethylene optionally substituted with one or more C_{1-3}alkyl, wherein the C_{1-3}alkyl is optionally substituted with one or more -OH or C_{1-3}alkoxy. In some embodiments, L^1 is selected from the group consisting of  , and  wherein, for each L^1, # denotes the point of attachment to L^2 and ## denotes the point of attachment to the remainder of the molecule. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

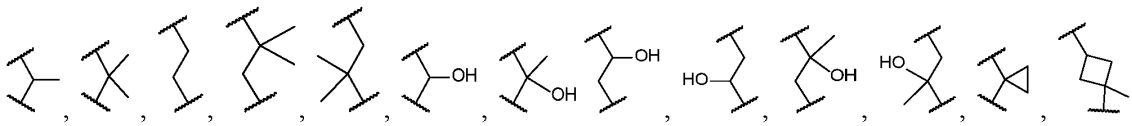
[0086] In some embodiments of a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1 is C_{1-6}alkylene optionally substituted with one or more deuterieum, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with -OH or C_{1-6}alkoxy. In some embodiments, L^1 is C_{1-3}alkylene optionally substituted with one or more deuterium, or C_{1-3}alkyl, wherein the C_{1-3}alkyl is optionally substituted with -OH or C_{1-3}alkoxy. In some embodiments, L^1 is methylene. In some embodiments, L^1 is ethylene. In some embodiments, L^1 is ethylene optionally substituted with one or more deuterium, or C_{1-3}alkyl, wherein the C_{1-3}alkyl is optionally substituted with one or more -OH or C_{1-3}alkoxy. In some embodiments, L^1 is selected from the group consisting of  ,  , and wherein, for each L^1, # denotes the point of attachment to L^2 and ## denotes the point of attachment to the remainder of the molecule.

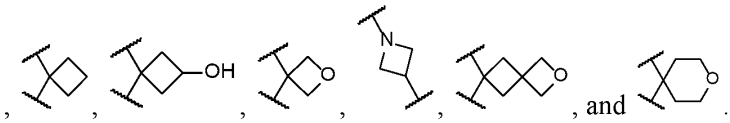
[0087] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^2 is O or N(R^x), wherein R^x is H or C_{1-6}alkyl. In some embodiments, L^2 is O or N(R^x), wherein R^x is H or C_{1-3}alkyl. In some

variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0088] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^2 is O. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

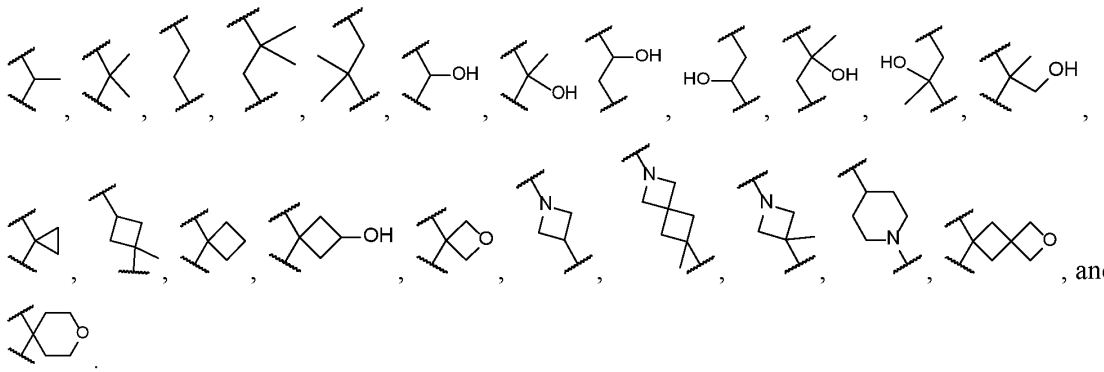
[0089] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is absent or is O, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or C_{1-6}alkylene, wherein the C_{1-6}alkylene of L^3 is optionally substituted with one or more C_{1-6}alkyl, the C_{3-10}cycloalkylof L^3 is optionally substituted with one or more -OH, and the 3-10 membered heterocyclyl of L^3 is optionally substituted with one or more -OH. In some embodiments, L^3 absent or is selected from the group consisting of O,  ,  , and . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0090] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is absent or is O, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or C_{1-6}alkylene, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more -OH, or C_{1-6}alkyl, the C_{1-6}alkylene of L^3 is optionally substituted with one or more -OH, or C_{1-6}alkyl, and the 3-10 membered heterocyclyl is optionally substituted with one or more -OH. In some embodiments, L^3 absent or is selected from the group consisting of O, 



. In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0091] In some embodiments of a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is absent or is O, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or C_{1-6}alkylene, wherein the C_{3-10}cycloalkyl of L^3 is optionally substituted with one or more -OH, or C_{1-6}alkyl; the C_{1-6}alkylene of L^3 is optionally substituted with one or more -OH, or C_{1-6}alkyl wherein the C_{1-6}alkyl is optionally substituted with one or more -OH; and the 3-10 membered heterocyclyl is optionally substituted with one or more -OH or C_{1-6}alkyl. In some embodiments, L^3 absent or is selected from the group consisting of O,

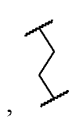
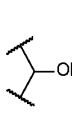
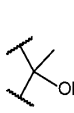
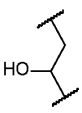
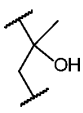
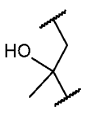


[0092] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is absent. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

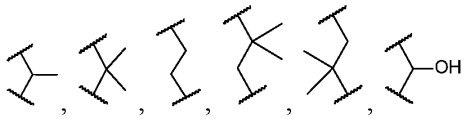
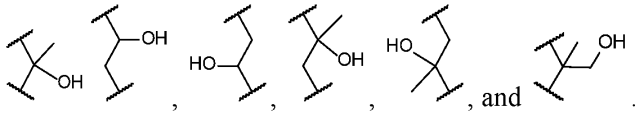
[0093] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is O. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer

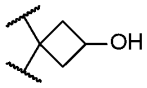
or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

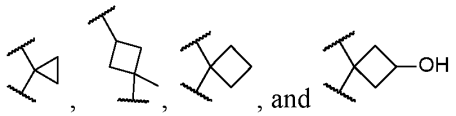
[0094] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is C_{1-6}alkylene. In some embodiments, L^3 is C_{1-3}alkylene. In some embodiments, L^3 is selected from the group consisting of  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0095] In some embodiments of a compound of formula (I), formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is C_{1-6}alkylene, wherein the C_{1-6}alkylene of L^3 is optionally substituted with one or more -OH, or C_{1-6}alkyl. In some embodiments, L^3 is C_{1-3}alkylene, wherein the C_{1-6}alkylene of L^3 is optionally substituted with one or more –OH, or C_{1-6}alkyl. In some embodiments, L^3 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

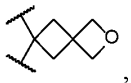
[0096] In some embodiments of a compound of formula (II) or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is C_{1-6}alkylene, wherein the C_{1-6}alkylene of L^3 is optionally substituted with one or more -OH, or C_{1-6}alkyl wherein the C_{1-6}alkyl is optionally substituted with one or more -OH. In some embodiments, L^3 is C_{1-3}alkylene, wherein the C_{1-6}alkylene of L^3 is optionally substituted with one or more -OH, or C_{1-6}alkyl. In some

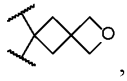
embodiments, L^3 is selected from the group consisting of  ,  , and .

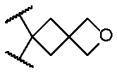
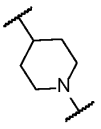
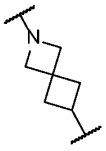
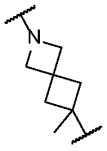
[0097] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of L^3 is optionally substituted with one or more -OH. In some embodiments, L^3 is C_{3-8}cycloalkyl, wherein the C_{3-8}cycloalkyl of L^3 is optionally substituted with one or more -OH. In some embodiments, L^3 is selected from the group consisting of  ,  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0098] In some embodiments of a compound of formula (I'), (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of L^3 is optionally substituted with one or more -OH. In some embodiments, L^3 is C_{3-8}cycloalkyl, wherein the C_{3-8}cycloalkyl of L^3 is optionally substituted with one or more -OH. In some embodiments, L^3 is selected from the group consisting of  , and . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

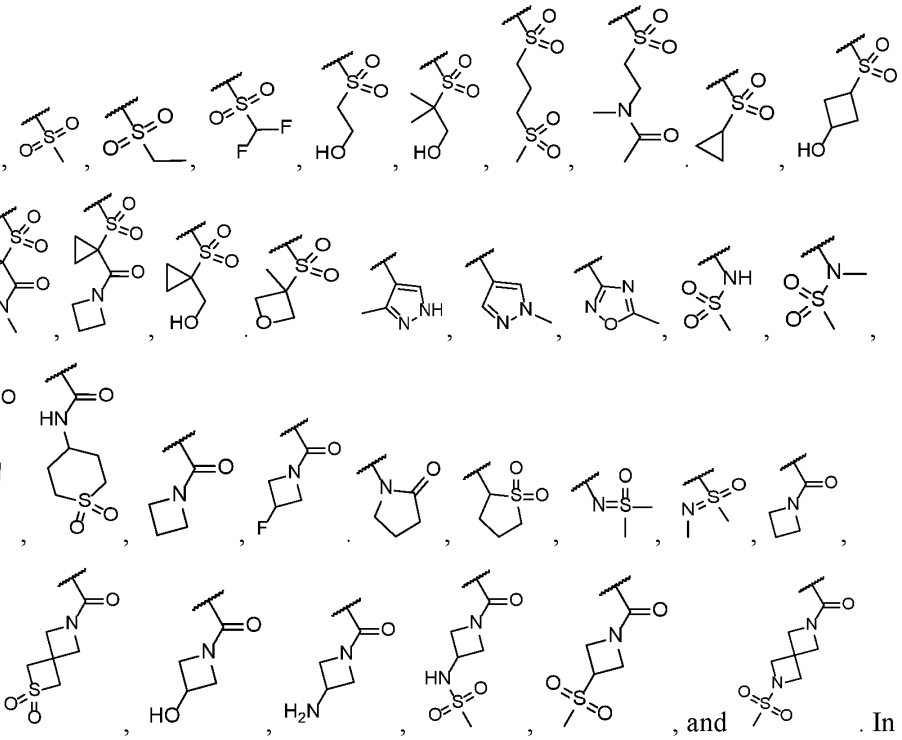
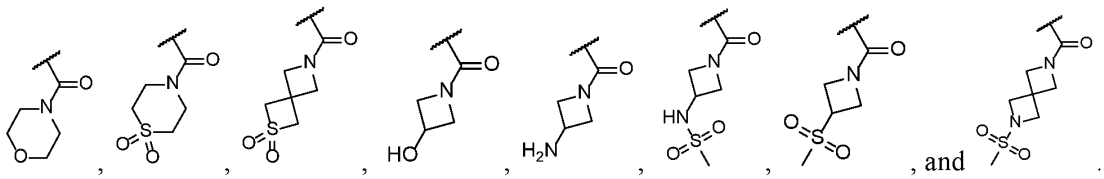
[0099] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is 3-10 membered heterocyclyl. In some embodiments, L^3 is 3-6 membered heterocyclyl. In some embodiments, L^3 is

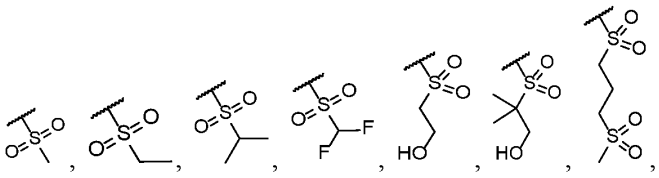
selected from the group consisting of  ,  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

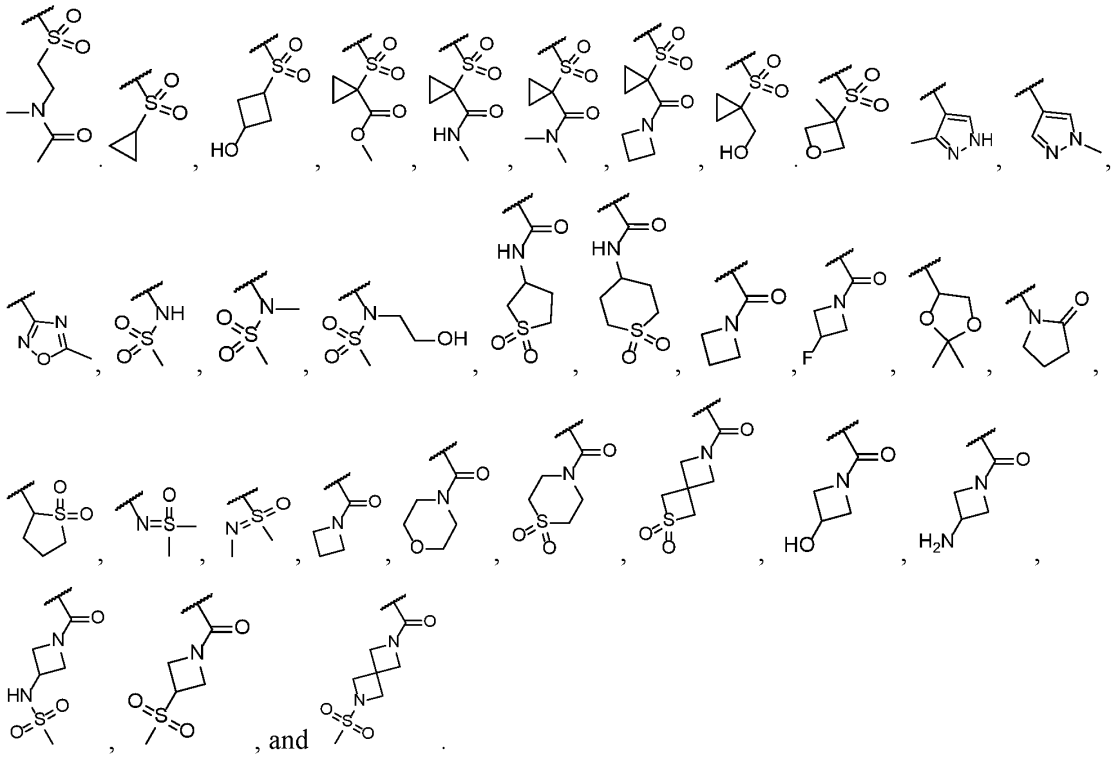
[0100] In some embodiments of a compound of formula (I), formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L3 is 3-10 membered heterocyclyl. In some embodiments, L^3 is 3-6 membered heterocyclyl. In some embodiments, L3 is selected from the group consisting of  ,  ,  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

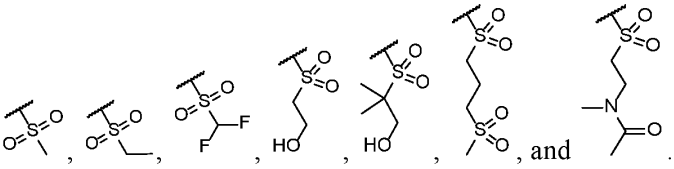
[0101] In some embodiments of a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L3 is 3-10 membered heterocyclyl. In some embodiments, L^3 is 3-6 membered heterocyclyl. In some embodiments, L3 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  , and  .

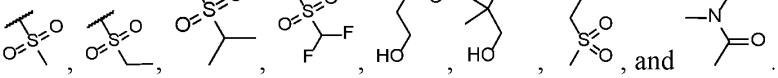
[0102] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing R^4 is $-S(O)_2-R^a$, 5-20 membered heteroaryl, $-N(R^d)_2$, $-NS(O)-(C_{1-6}alkyl)_2$, $-C(O)-N(R^e)_2$, 3-10 membered heterocyclyl, $-S(O)(N-C_{1-6}alkyl)-(C_{1-6}alkyl)$, or -CN. In some embodiments, R^4 is $S(O)_2-R^a$, 5-10 membered heteroaryl, $-N(R^d)_2$, $-NS(O)-(C_{1-3}alkyl)_2$, $-C(O)-N(R^e)_2$, 3-6 membered heterocyclyl, $-S(O)(N-C_{1-3}alkyl)-(C_{1-3}alkyl)$, or -CN. In some embodiments, R^4 is selected from the group consisting of $-NH_2$,

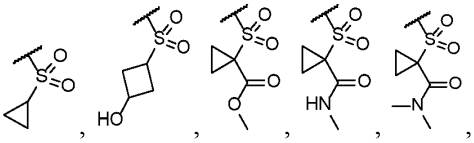
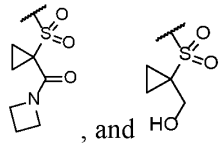
-CN, -C(O)-N(CH3)2,  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0103] In some embodiments of a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing R^4 is $-S(O)_2-R^a$, 5-20 membered heteroaryl, $-N(R^d)_2$, $-NS(O)-(C_{1-6}alkyl)_2$, $-C(O)-N(R^e)_2$, 3-10 membered heterocyclyl, $-S(O)-N(C_{1-6}alkyl)-(C_{1-6}alkyl)$, -CN, $-(CH_2)_qOH$, $-C(O)-C_{1-6}alkyl$, or $-P(O)(C_{1-6}alkyl)_2$. In some embodiments, R^4 is $S(O)_2-R^a$, 5-10 membered heteroaryl, $-N(R^d)_2$, $-NS(O)-(C_{1-3}alkyl)_2$, $-C(O)-N(R^e)_2$, 3-6 membered heterocyclyl, $-S(O)(N-C_{1-3}alkyl)-(C_{1-3}alkyl)$, -CN, -OH, $-CH_2OH$, $-C(O)-C_{1-3}alkyl$, or $-P(O)(C_{1-3}alkyl)_2$. In some embodiments, R^4 is selected from the group consisting of $-NH_2$, -CN, -OH, $-CH_2OH$, $-C(O)-N(CH_3)_2$,  ,

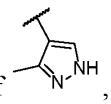
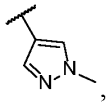


[0104] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is $-S(O)_2-R^a$, wherein R^a is C_{1-6}alkyl. In some embodiments, R^4 is $-S(O)_2-R^a$, wherein R^a is C_{1-6}alkyl optionally substituted with one or more halo, -OH, $-S(O)_2-C_{1-6}$alkyl, or $-N(C_{1-6}alkyl)-C(O)-C_{1-6}$alkyl. In some embodiments, R^4 is $-S(O)_2-R^a$, wherein R^a is C_{1-3}alkyl optionally substituted with one or more halo, -OH, $-S(O)_2-C_{1-3}$alkyl, or $-N(C_{1-3}alkyl)-C(O)-C_{1-3}$alkyl. In some embodiments, R^4 is selected from the group consisting of  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

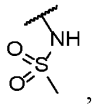
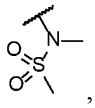
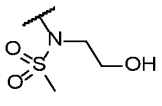
[0105] In some embodiments of a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is -$S(O)_2$-R^a, wherein R^a is C_{1-6}alkyl. In some embodiments, R^4 is -$S(O)_2$-R^a, wherein R^a is C_{1-6}alkyl optionally substituted with one or more halo, -OH, -$S(O)_2$-C_{1-6}alkyl, or -N(C_{1-6}alkyl)-C(O)-C_{1-6}alkyl. In some embodiments, R^4 is -$S(O)_2$-R^a, wherein R^a is C_{1-3}alkyl optionally substituted with one or more halo, -OH, -$S(O)_2$-C_{1-3}alkyl, or -N(C_{1-3}alkyl)-C(O)-C_{1-3}alkyl. In some embodiments, R^4 is selected from the group consisting of  .

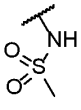
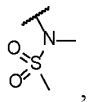
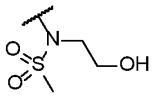
[0106] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is -$S(O)_2$-R^a, wherein R^a is C_{3-10}cycloalkyl. In some embodiments, R^4 is -$S(O)_2$-R^a, wherein R^a is C_{3-10}cycloalkyl optionally substituted with one or more -OH, C(O)$_2$-C_{1-6}alkyl, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, –C(O)-C_{3-10}heterocyclyl or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more -OH. In some embodiments, R^4 is -$S(O)_2$-R^a, wherein R^a is C_{3-6}cycloalkyl optionally substituted with one or more -OH, C(O)$_2$-C_{1-6}alkyl, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, –C(O)-C_{3-10}heterocyclyl, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more -OH. In some embodiments, R^4 is -$S(O)_2$-R^a, wherein R^a is C_{3-6}cycloalkyl optionally substituted with one or more -OH, C(O)$_2$-C_{1-3}alkyl, -C(O)-NH(C_{1-3}alkyl), -C(O)-N(C_{1-3}alkyl)$_2$, –C(O)-C_{3-6}heterocyclyl, or C_{1-3}alkyl, wherein the C_{1-3}alkyl is optionally substituted with one or more -OH. In some embodiments, R^4 is selected from the group consisting of  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0107] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is $-S(O)_2-R^a$, wherein R^a is 3-10 membered heterocyclyl. In some embodiments R^4 is $-S(O)_2-R^a$, wherein R^a is 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl. In some embodiments, R^4 is $-S(O)_2-R^a$, wherein R^a is 3-6 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl. In some embodiments, wherein R^4 is $-S(O)_2-R^a$, wherein R^a is 3-6 membered heterocyclyl optionally substituted with one or more C_{1-3}alkyl. In some embodiments, R^4 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0108] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is 5-20 membered heteroaryl. In some embodiments, R^4 is 5-20 membered heteroaryl optionally substituted with one or more C_{1-6}alkyl. In some embodiments, R^4 is 5-6 membered heteroaryl optionally substituted with one or more C_{1-6}alkyl. In some embodiments, R^4 is 5-6 membered heteroaryl optionally substituted with one or more C_{1-3}alkyl. In some embodiments, R^4 is 5-6 membered heteroaryl optionally substituted with one or more methyl. In some embodiments, R^4 is selected from the group consisting of  ,  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

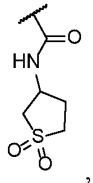
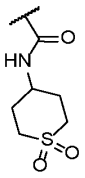
[0109] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is $-N(R^d)_2$, wherein each of R^d is independently H, C_{1-6} alkyl, or $-S(O)_2-R^a$, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more -OH, and wherein R^a is C_{1-6}alkyl. In some embodiments, R^4 is $-N(R^d)_2$, wherein each of R^d is independently H, C_{1-3} alkyl, or $-S(O)_2-R^a$, wherein the C_{1-3}alkyl of R^d is optionally substituted with one or more -OH, and wherein R^a is C_{1-3}alkyl. In some embodiments, R^4 is $-N(R^d)_2$, wherein each of R^d is independently H, C_{1-6} alkyl, or $-S(O)_2-R^a$, wherein the C_{1-3}alkyl of R^d is

optionally substituted with one or more -OH, and wherein R^a is methyl. In some embodiments, R^4 is selected from the group consisting of $-NH_2$,  ,  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

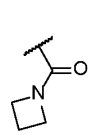
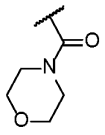
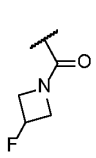
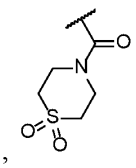
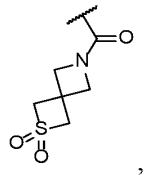
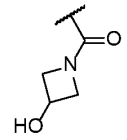
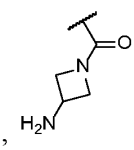
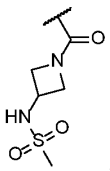
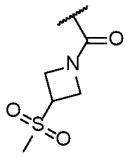
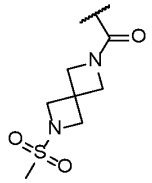
[0110] In some embodiments of a compound of formula (I), formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is $-N(R^d)_2$, wherein each of R^d is independently H, C_{1-6} alkyl, or $-S(O)_2-R^a$, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more -OH, and wherein R^a is C_{1-6}alkyl. In some embodiments, R^4 is $-N(R^d)_2$, wherein each of R^d is independently H, C_{1-3} alkyl, or $-S(O)_2-R^a$, wherein the C_{1-3}alkyl of R^d is optionally substituted with one or more -OH, and wherein R^a is C_{1-3}alkyl. In some embodiments, R^4 is $-N(R^d)_2$, wherein each of R^d is independently H, C_{1-6} alkyl, or $-S(O)_2-R^a$, wherein the C_{1-3}alkyl of R^d is optionally substituted with one or more -OH, and wherein R^a is methyl. In some embodiments, R^4 is selected from the group consisting of $-NH_2$,  ,  ,  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0111] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is $-C(O)-N(R^e)_2$, wherein each of R^e is independently H or C_{1-6} alkyl. In some embodiments, R^4 is $-C(O)-N(R^e)_2$, wherein each of R^e is independently H or C_{1-3} alkyl. In some embodiments, R^4 is $-C(O)-N(R^e)_2$, wherein each of R^e is independently H or methyl. In some embodiments, R^4 is $-C(O)-NH_2$. In some embodiments, R^4 is $-C(O)-NH(CH_3)$. In some embodiments, R^4 is $-C(O)-N(CH_3)_2$. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or

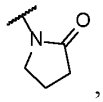
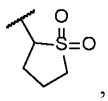
tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0112] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is -C(O)-N(R^e)$_2$, wherein each of R^e is independently H or 3-10 membered heterocycle, wherein the 3-10 membered heterocycle is optionally substituted with one or more oxo. In some embodiments, R^4 is -C(O)-N(R^e)$_2$, wherein each of R^e is independently H or 3-6 membered heterocycle, wherein the 3-6 membered heterocycle is optionally substituted with one or more oxo. In some embodiments, R^4 is selected from the group consisting of  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

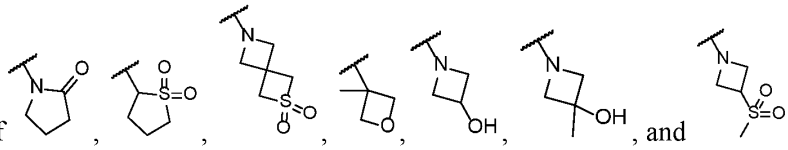
[0113] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is -C(O)-N(R^e)$_2$, wherein both R^e together with the N to which they are attached are taken together to form a 3-10 membered heterocyclyl. In some embodiments R^4 is -C(O)-N(R^e)$_2$, wherein both R^e together with the N to which they are attached are taken together to form a 3-10 membered heterocyclyl, wherein the 3-10 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, -NH_2, -NH-S(O)$_2$-R^a, or -S(O)$_2$-R^a, wherein R^a is C_{1-6}alkyl. In some embodiments R^4 is -C(O)-N(R^e)$_2$, wherein both R^e together with the N to which they are attached are taken together to form a 3-7 membered heterocyclyl, wherein the 3-7 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, NH-S(O)$_2$-R^a, or -S(O)$_2$-R^a, wherein R^a is C_{1-3}alkyl. In some embodiments R^4 is -C(O)-N(R^e)$_2$, wherein both R^e together with the N to which they are attached are taken together to form a 3-7 membered heterocyclyl, wherein the 3-7 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, -NH_2, -NH-S(O)$_2$-R^a, or -S(O)$_2$-R^a, wherein R^a is

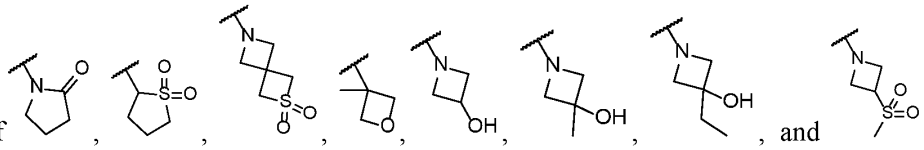
methyl. In some embodiments, R^4 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

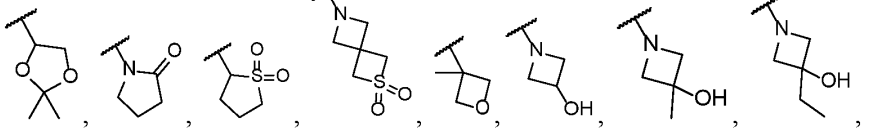
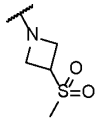
[0114] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is 3-10 membered heterocyclyl optionally substituted with one or more oxo or C_{1-6}alkyl. In some embodiments, R^4 is 3-7 membered heterocyclyl optionally substituted with one or more oxo or C_{1-6}alkyl. In some embodiments, R^4 is 3-7 membered heterocyclyl optionally substituted with one or more oxo or C_{1-3}alkyl. In some embodiments, R^4 is selected from the group consisting of  ,  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

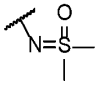
[0115] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl, -OH, oxo or $-S(O)_2R^a$. In some embodiments, R^4 is 3-7 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl, -OH, oxo or $-S(O)_2R^a$. In some embodiments, R^4 is 3-7 membered heterocyclyl optionally substituted with one or more C_{1-3}alkyl, -OH, oxo or $-S(O)_2R^a$. In some embodiments, R^4 is selected from the

group consisting of  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0116] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl, -OH, oxo or $-S(O)_2R^a$. In some embodiments, R^4 is 3-7 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl, -OH, oxo or $-S(O)_2R^a$. In some embodiments, R^4 is 3-7 membered heterocyclyl optionally substituted with one or more C_{1-3}alkyl, -OH, oxo or $-S(O)_2R^a$. In some embodiments, R^4 is selected from the group consisting of  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

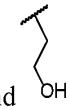
[0117] In some embodiments of a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl, -OH , oxo or $-S(O)_2R^a$. In some embodiments, R^4 is 3-7 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl, -OH, oxo or $-S(O)_2R^a$. In some embodiments, R^4 is 3-7 membered heterocyclyl optionally substituted with one or more C_{1-3}alkyl, -OH, oxo or $-S(O)_2R^a$. In some embodiments, R^4 is selected from the

group consisting of  , and  .

[0118] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is -NS(O)-(C_{1-6}alkyl)$_2$. In some embodiments, R^4 is -NS(O)-(C_{1-3}alkyl)$_2$. In some embodiments, R^4 is  .

[0119] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is -S(O)(N-C_{1-6}alkyl)-(C_{1-6}alkyl). In some embodiments, R^4 is -S(O)(N-C_{1-3}alkyl)-(C_{1-3}alkyl). In some embodiments, R^4 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0120] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is -CN. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0121] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is -$(CH_2)_q$OH, wherein q is an integer from 0-6. R^4 is -$(CH_2)_q$OH, wherein q is an integer from 0-2. In some embodiments, R^4 is -OH. In some embodiments, R^4 is selected from the group consisting of  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a

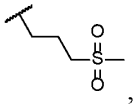
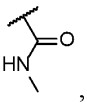
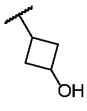
stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0122] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is -C(O)-C_{1-6}alkyl. In some embodiments, R^4 is -C(O)-C_{1-3}alkyl. In some embodiments, R^4 is -C(O)CH_3. In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

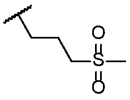
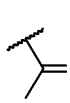
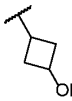
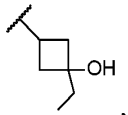
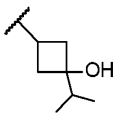
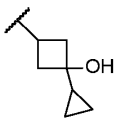
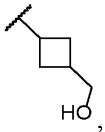
[0123] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is -P(O)(C_{1-6}alkyl)$_2$. In some embodiments, R^4 is -P(O)(C_{1-3}alkyl)$_2$. In some embodiments, R^4 is -P(O)(CH_3)$_2$. In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0124] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, each of X^1 and X^2 is independently N or C(R^5). In some embodiments, each of X^1 and X^2 is N. In some embodiments, each of X^1 and X^2 is C(R^5). In some embodiments, one of X^1 and X^2 is CR^5, and the other of X^1 and X^2 is N. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

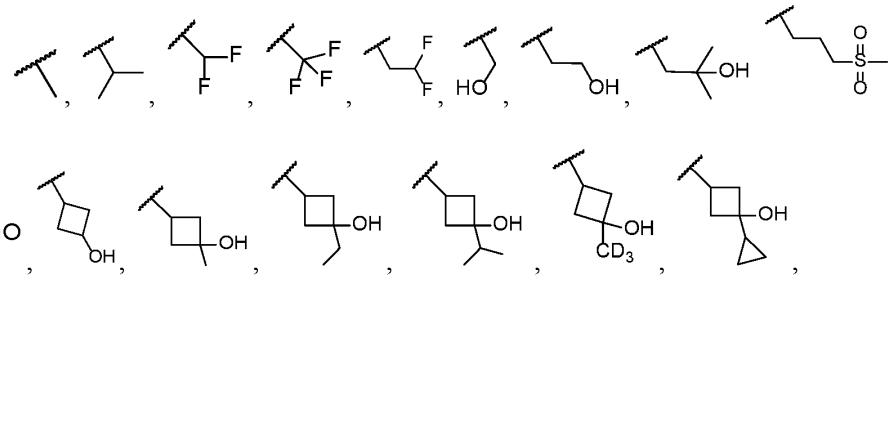
[0125] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, one of X^1 and X^2 is CR^5, and the other of X^1 and X^2 is C that is taken together with R^4, and the atoms to which they are attached, to form a 5-10 membered heterocyclyl optionally substituted with one or more of R^b. In some embodiments, one of X^1 and X^2 is CR^5, and the other of X^1 and X^2 is C that is taken together with R^4, and the atoms to which they are attached, to form a 5-8 membered heterocyclyl optionally substituted with one or more of R^b. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0126] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^b is halo, oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -S(O)$_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, OH, or -S(O)$_2$-C_{1-6}alkyl, and the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more -OH. In some embodiments, R^b is halo, oxo, C_{1-3}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-3}alkyl), -C(O)-N(C_{1-3}alkyl)$_2$, -S(O)$_2$-R^a, C_{3-6}cycloalkyl, and 3-6 membered heterocyclyl, wherein the C_{1-3}alkyl of R^b is optionally substituted with one or more halo, OH, or -S(O)$_2$-C_{1-3}alkyl, and the C_{3-6}cycloalkyl of R^b is optionally substituted with one or more -OH. In some embodiments, R^b is selected from the group consisting of oxo, -S(O)$_2$CH$_3$,  ,  ,  ,  ,  ,  ,  ,  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

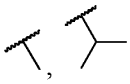
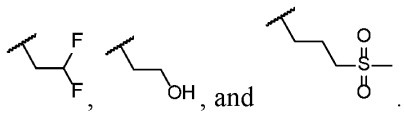
[0127] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^b is, independently at each occurrence, selected from the group consisting of halo, oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -S(O)$_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, OH, -S(O)$_2$-C_{1-6}alkyl, or C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of the C_{1-6}alkyl of R^b is further optionally substituted with one or more C_{1-6}alkyl or -OH, and the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more -OH, C_{3-10}cycloalkyl, or C_{1-6}alkyl, wherein the C_{1-6}alkyl of the C_{3-10}cycloalkyl of R^b is further optionally substituted with one or more -OH. In some embodiments, R^b is, independently at each occurrence, selected from the group consisting of halo, oxo, C_{1-3}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-3}alkyl), -C(O)-N(C_{1-3}alkyl)$_2$, -S(O)$_2$-R^a, C_{3-6}cycloalkyl, and 3-6 membered heterocyclyl, wherein the C_{1-3}alkyl of R^b is optionally substituted with one or more halo, OH, -S(O)$_2$-C_{1-3}alkyl, or C_{3-6}cycloalkyl, wherein the C_{3-6}cycloalkyl of the C_{1-3}alkyl of R^b is further optionally substituted with one or more C_{1-3}alkyl or -OH, and the C_{3-6}cycloalkyl of R^b is

optionally substituted with one or more -OH, C_{3-6}cycloalkyl, or C_{1-3}alkyl, wherein the C_{1-3}alkyl of the C_{3-6}cycloalkyl of R^b is further optionally substituted with one or more -OH. In some embodiments, R^b is selected from the group consisting of oxo, $-S(O)_2CH_3$,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0128] In some embodiments of a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^b is, independently at each occurrence, selected from the group consisting of -OH, halo, oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, $-S(O)_2-R^a$, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, OH, $-S(O)_2-C_{1-6}$alkyl, or C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of the C_{1-6}alkyl of R^b is further optionally substituted with one or more C_{1-6}alkyl or -OH, and the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more -OH, C_{3-10}cycloalkyl, or C_{1-6}alkyl, wherein the C_{1-6}alkyl of the C_{3-10}cycloalkyl of R^b is further optionally substituted with one or more -OH, deuterium, or halo. In some embodiments, R^b is, independently at each occurrence, selected from the group consisting of -OH, halo, oxo, C_{1-3}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-3}alkyl), -C(O)-N(C_{1-3}alkyl)$_2$, $-S(O)_2-R^a$, C_{3-6}cycloalkyl, and 3-6 membered heterocyclyl, wherein the C_{1-3}alkyl of R^b is optionally substituted with one or more halo, OH, $-S(O)_2-C_{1-3}$alkyl, or C_{3-6}cycloalkyl, wherein the C_{3-6}cycloalkyl of the C_{1-3}alkyl of R^b is further optionally substituted with one or more C_{1-3}alkyl or -OH, and the C_{3-6}cycloalkyl of R^b is optionally substituted with one or more -OH, C_{3-6}cycloalkyl, or C_{1-3}alkyl, wherein the C_{1-3}alkyl of the C_{3-6}cycloalkyl of R^b is further optionally substituted with one or more -OH, deuterium or halo. In some embodiments, R^b is selected from the group consisting of -

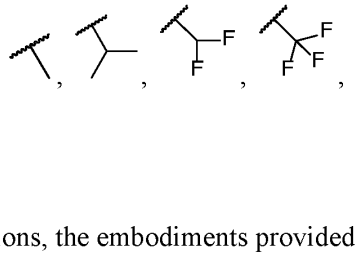
OH, oxo, -S(O)$_2$CH$_3$, 

[0129] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^b is oxo. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

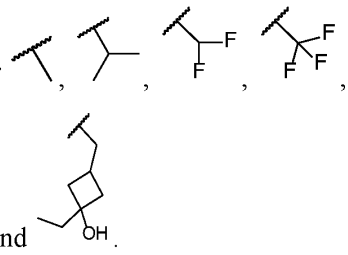
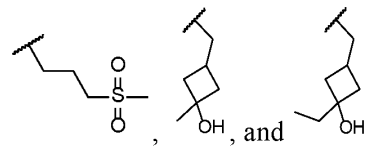
[0130] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^b is C_{1-6}alkyl. In some embodiments, R^b is C_{1-6}alkyl optionally substituted with one or more halo, OH, or -S(O)$_2$-C_{1-6}alkyl. In some embodiments, R^b is C_{1-3}alkyl optionally substituted with one or more more halo, OH , or -S(O)$_2$-C_{1-3}alkyl. In some embodiments, R^b is selected from the group consisting of  ,  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0131] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^b is C_{1-6}alkyl. In some embodiments, the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, OH, -S(O)$_2$-C_{1-6}alkyl, or C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of the C_{1-6}alkyl of R^b is further optionally substituted with one or more C_{1-6}alkyl or -OH. In some embodiments, R^b is C_{1-3}alkyl optionally

substituted with one or more halo, OH, -S(O)$_2$-C$_{1-3}$alkyl, or C$_{3-6}$cycloalkyl, wherein the C$_{3-6}$cycloalkyl of the C$_{1-3}$alkyl of R^b is further optionally substituted with one or more C$_{1-3}$alkyl or -OH.

In some embodiments, R^b is selected from the group consisting of  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

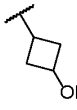
[0132] In some embodiments of a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^b is C$_{1-6}$alkyl. In some embodiments, the C$_{1-6}$alkyl of R^b is optionally substituted with one or more halo, OH, -S(O)$_2$-C$_{1-6}$alkyl, or C$_{3-10}$cycloalkyl, wherein the C$_{3-10}$cycloalkyl of the C$_{1-6}$alkyl of R^b is further optionally substituted with one or more C$_{1-6}$alkyl or -OH. In some embodiments, R^b is C$_{1-3}$alkyl optionally substituted with one or more halo, OH, -S(O)$_2$-C$_{1-3}$alkyl, or C$_{3-6}$cycloalkyl, wherein the C$_{3-6}$cycloalkyl of the C$_{1-3}$alkyl of R^b is further optionally substituted with one or more C$_{1-3}$alkyl or -OH.

In some embodiments, R^b is selected from the group consisting of  , and  .

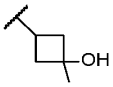
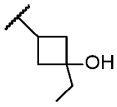
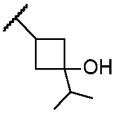
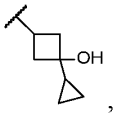
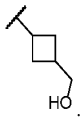
[0133] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^b is -C(O)-NH(C$_{1-6}$alkyl). In some embodiments, R^b is -C(O)-NH(C$_{1-3}$alkyl). In some embodiments, R^b is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

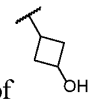
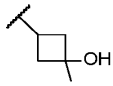
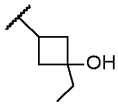
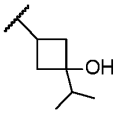
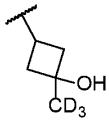
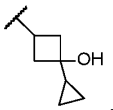
[0134] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^b is -C(O)-C_{1-6}alkyl. In some embodiments, R^b is -C(O)-C_{1-3}alkyl. In some embodiments, R^b is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0135] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing R^b is -$S(O)_2$-R^a, wherein R^a is C_{1-6}alkyl. In some embodiments, R^b is -$S(O)_2$-R^a, wherein R^a is C_{1-3}alkyl. In some embodiments, R^b is -$S(O)_2$-R^a, R^a is methyl. In some embodiments, R^b is -$S(O)_2CH_3$. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0136] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^b is C_{3-10}cycloalkyl optionally substituted with one or more –OH. In some embodiments, R^b is C_{3-6}cycloalkyl optionally substituted with one or more –OH. In some embodiments, R^b is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0137] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^b is C_{3-10}cycloalkyl optionally substituted with one or more -OH, C_{3-10}cycloalkyl, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is further optionally substituted with one or more –OH. In some embodiments, R^b is C_{3-6}cycloalkyl optionally substituted with one or more -OH, C_{3-6}cycloalkyl, or C_{1-3}alkyl, wherein the C_{1-3}alkyl is further optionally substituted with one or more –OH. In some embodiments, R^b is selected from the

group consisting of  ,  ,  ,  ,  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

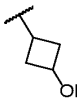
[0138] In some embodiments of a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^b is C_{3-10}cycloalkyl optionally substituted with one or more -OH, C_{3-10}cycloalkyl, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is further optionally substituted with one or more -OH, deuterium, or halo. In some embodiments, R^b is C_{3-6}cycloalkyl optionally substituted with one or more -OH, C_{3-6}cycloalkyl, or C_{1-3}alkyl, wherein the C_{1-3}alkyl is further optionally substituted with one or more -OH, deuterium, or halo. In some embodiments, R^b is selected from the group consisting of  ,  ,  ,  ,  ,  , and  .

[0139] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^b is 3-10 membered heterocyclyl. In some embodiments, R^b is 3-6 membered heterocyclyl. In some embodiments, R^b is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0140] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, one of X^1 and X^2 is CR^5, and the other of X^1 and X^2 is C that is taken together with R^4, and the atoms to which they are attached, to form a 5-10 membered heteroaryl. In some embodiments, one of X^1 and X^2 is CR^5, and the other of X^1 and X^2 is C that is taken together with R^4, and the atoms to which they are attached, to form a

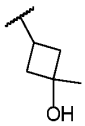
5-6 membered heteroaryl. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

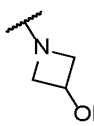
[0141] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, one of X^1 and X^2 is CR^5, and the other of X^1 and X^2 is C that is taken together with R^4, and the atoms to which they are attached, to form a 5-10 membered heteroaryl optionally substituted with one or more R^c. In some embodiments one of X^1 and X^2 is CR^5, and the other of X^1 and X^2 is C that is taken together with R^4, and the atoms to which they are attached, to form a 5-6 membered heteroaryl optionally substituted with one or more R^c. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

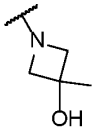
[0142] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^c is halo, $C_{1\text{-}6}$alkyl, -C(O)-$C_{1\text{-}6}$alkyl, -C(O)-NH_2, -C(O)-NH($C_{1\text{-}6}$alkyl), -C(O)-N($C_{1\text{-}6}$alkyl)$_2$, -$S(O)_2$-R^a, $C_{3\text{-}10}$cycloalkyl, and 3-10 membered heterocyclyl, wherein the $C_{1\text{-}6}$alkyl of R^c is optionally substituted with one or more -$S(O)_2$-$C_{1\text{-}6}$alkyl, and the $C_{3\text{-}10}$cycloalkyl of R^c is optionally substituted with one or more -OH. In some embodiments, R^c is halo, $C_{1\text{-}3}$alkyl, -C(O)-$C_{1\text{-}3}$alkyl, -C(O)-NH_2, -C(O)-NH($C_{1\text{-}3}$alkyl), -C(O)-N($C_{1\text{-}3}$alkyl)$_2$, -$S(O)_2$-R^a, $C_{3\text{-}6}$cycloalkyl, and 3-6 membered heterocyclyl, wherein the $C_{1\text{-}6}$alkyl of R^c is optionally substituted with one or more -$S(O)_2$-$C_{1\text{-}3}$alkyl, and the $C_{3\text{-}6}$cycloalkyl of R^c is optionally substituted with one or more -OH. In some embodiments, R^c is selected from the group consisting of methyl, isopropyl, -$S(O)_2CH_3$, and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0143] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^c is independently at each occurrence, selected from the group consisting of halo, $C_{1\text{-}6}$alkyl, -C(O)-$C_{1\text{-}6}$alkyl, -C(O)-NH_2, -

C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -S(O)$_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein the C_{1-6}alkyl of R^c is optionally substituted with one or more -S(O)$_2$-C_{1-6}alkyl, the C_{3-10}cycloalkyl of R^c is optionally substituted with one or more –OH, or C_{1-6}alkyl, and the 3-10 membered heterocyclyl of R^c is optionally substituted with one or more -OH, or C_{1-6}alkyl,wherein the C_{1-6}alkyl is further optionally substituted with one or more -OH. In some embodiments, R^c is independently at each occurrence, selected from the group consisting of halo, C_{1-3}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-NH$_2$, -C(O)-NH(C_{1-3}alkyl), -C(O)-N(C_{1-3}alkyl)$_2$, -S(O)$_2$-R^a, C_{3-6}cycloalkyl, and 3-6 membered heterocyclyl, wherein the C_{1-3}alkyl of R^c is optionally substituted with one or more -S(O)$_2$-C_{1-3}alkyl, the C_{3-6}cycloalkyl of R^c is optionally substituted with one or more –OH, or C_{1-3}alkyl, and the 3-6 membered heterocyclyl of R^c is optionally substituted with one or more -OH, or C_{1-3}alkyl,wherein the C_{1-3}alkyl is further optionally substituted with one or more -OH. In some embodiments, R^c is selected from the group consisting of methyl, isopropyl, -S(O)$_2$CH$_3$, and 

, 

, 

, 

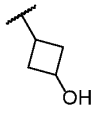
, and 

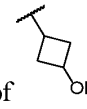
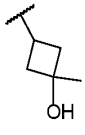
. In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0144] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^c is C_{1-6}alkyl, -S(O)$_2$-R^a. In some embodiments, R^c is C_{1-3}alkyl. In some embodiments, R^c is methyl. In some embodiments, R^c is isopropyl. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0145] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^c is C_{1-6}alkyl optionally substituted with one or more -S(O)$_2$-R^a, wherein R^a is C_{1-6}alkyl. In some embodiments, R^c is C_{1-3}alkyl optionally substituted with one or more -S(O)$_2$-R^a, wherein R^a is C_{1-3}alkyl. In some embodiments, R^c is C_{1-3}alkyl optionally substituted with one or more -S(O)$_2$-R^a, wherein R^a is

methyl. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0146] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^c is C_{3-10}cycloalkyl optionally substituted with one or more -OH. In some embodiments, R^c is C_{3-6}cycloalkyl optionally substituted with one or more -OH. In some embodiments, R^c is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0147] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^c is C_{3-10}cycloalkyl optionally substituted with one or more -OH, or C_{1-6}alkyl. In some embodiments, R^c is C_{3-6}cycloalkyl optionally substituted with one or more -OH, or C_{1-3}alkyl. In some embodiments, R^c is selected from the group consisting of  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0148] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^c is 3-10 membered heterocyclyl optionally substituted with one or more -OH, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is further optionally substituted with one or more -OH. In some embodiments, R^c is 3-6 membered heterocyclyl optionally substituted with one or more -OH, or C_{1-3}alkyl, wherein the C_{1-3}alkyl is further optionally substituted with one or more -OH. In some embodiments, R^c is selected from the group consisting of  ,  , and  . In some variations, the embodiments provided

herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

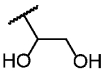
[0149] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^5 is independently at each occurrence, H, halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH and wherein the C_{1-6}alkoxy is optionally substituted with one or more halo. In some embodiments, R^5 is independently at each occurrence, H, halo, -CN, 3-6 membered heterocyclyl, C_{1-3}alkyl, or C_{1-3}alkoxy, wherein the C_{1-3}alkyl of R^5 is optionally substituted with one or more halo, or -OH and wherein the C_{1-3}alkoxy is optionally substituted with one or more halo. In some embodiments, R^5 is selected from the group consisting of H, Cl, F, -CN, , , , , and . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0150] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^5 is H. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

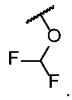
[0151] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^5 is halo. In some embodiments, R^5 is Cl, or F. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0152] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^5 is -CN. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer

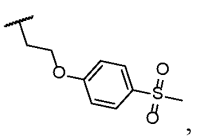
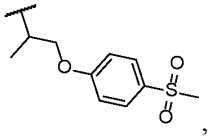
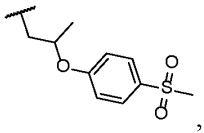
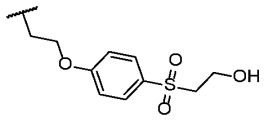
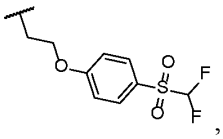
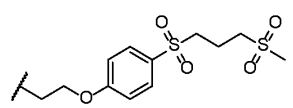
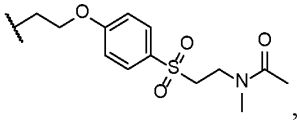
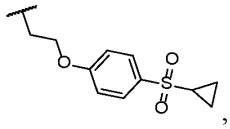
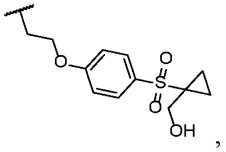
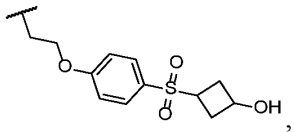
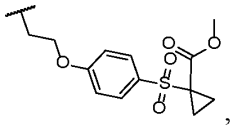
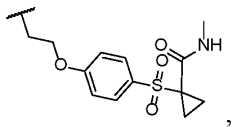
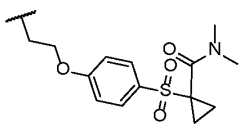
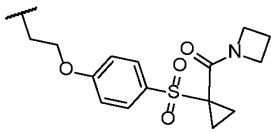
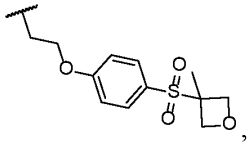
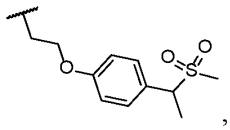
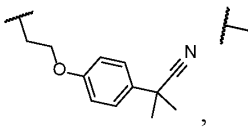
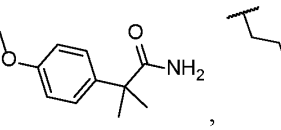
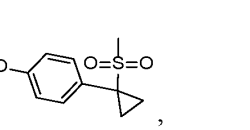
or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

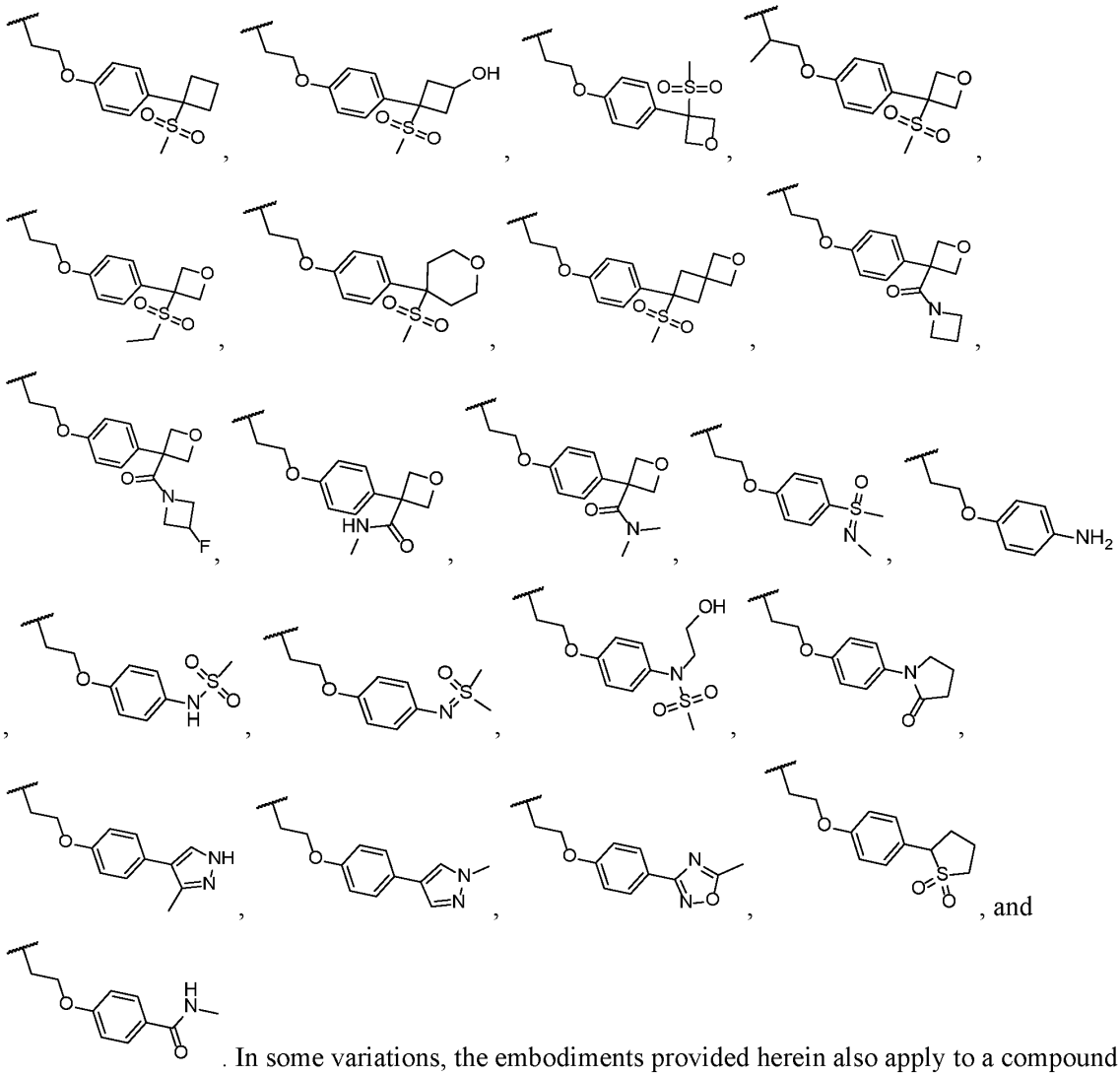
[0153] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^5 is C_{1-6}alkyl. In some embodiments, R^5 is C_{1-3}alkyl. In some embodiments, R^5 is methyl. In some embodiments, R^5 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH. In some embodiments, R^5 is C_{1-3}alkyl, wherein the C_{1-3}alkyl of R^5 is optionally substituted with one or more halo, or -OH. In some embodiments, R^5 is C_{1-3}alkyl, wherein the C_{1-3}alkyl of R^5 is optionally substituted with one or more fluoro, or -OH. In some embodiments, R^5 is independently selected from the group consisting of methyl,  ,  ,  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0154] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^5 is 3-10 membered heterocyclyl. In some embodiments, R^5 is 3-6 membered heterocyclyl. In some embodiments, R^5 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0155] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^5 is C_{1-6}alkoxy optionally substituted with one or more halo. In some embodiments, R^5 is C_{1-3}alkoxy optionally substituted with one or more halo. In some embodiments, R^5 is C_{1-3}alkoxy optionally substituted with one or more fluoro. In some embodiments, R^5 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

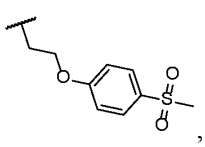
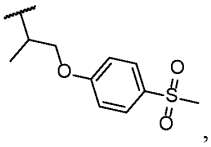
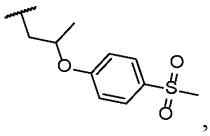
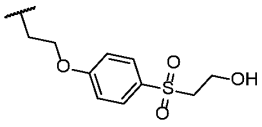
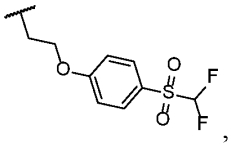
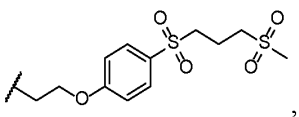
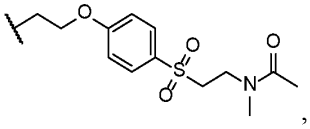
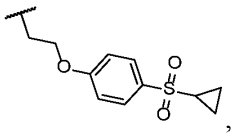
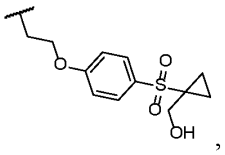
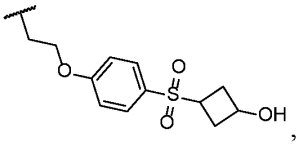
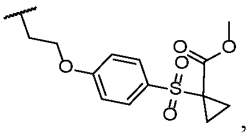
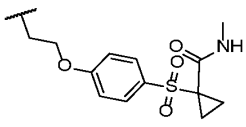
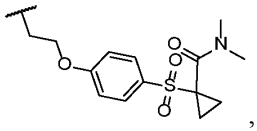
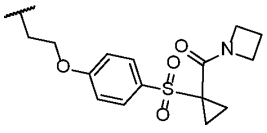
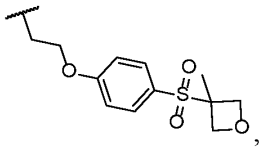
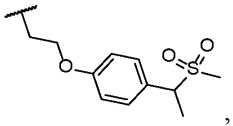
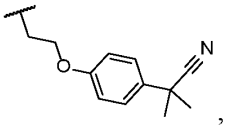
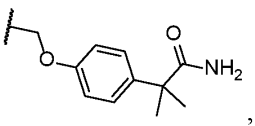
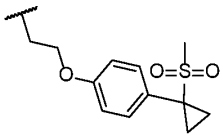
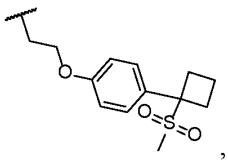
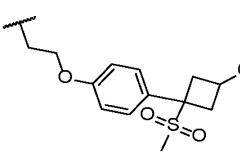
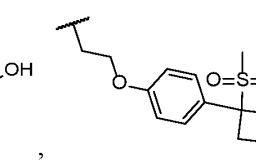
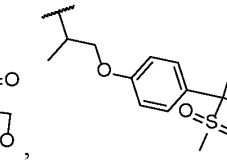
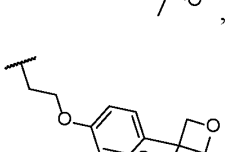
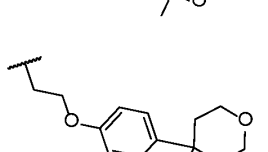
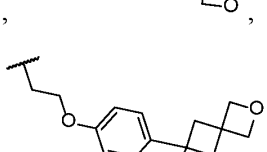
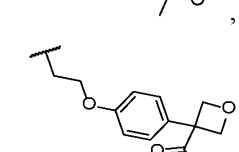
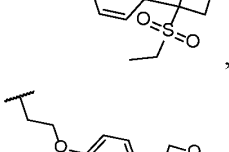
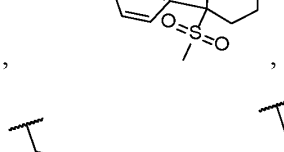
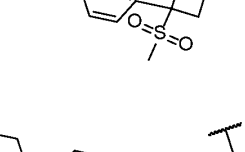
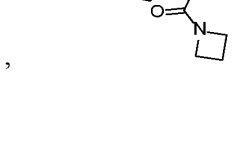
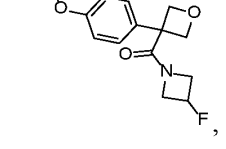
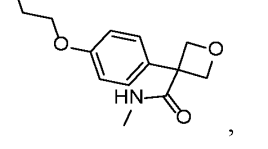
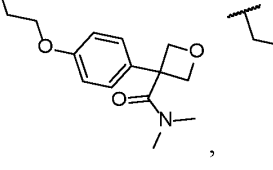
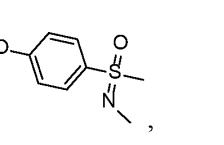
[0156] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^6 and R^7 are each independently H or halo. In some embodiments, R^6 and R^7 are each independently H or fluoro. In some embodiments, each of R^6 and R^7 is H. In some embodiments, each of R^6 and R^7 is fluoro. In some embodiments, one of R^6 and R^7 is H and the other of R^6 and R^7 is fluoro. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

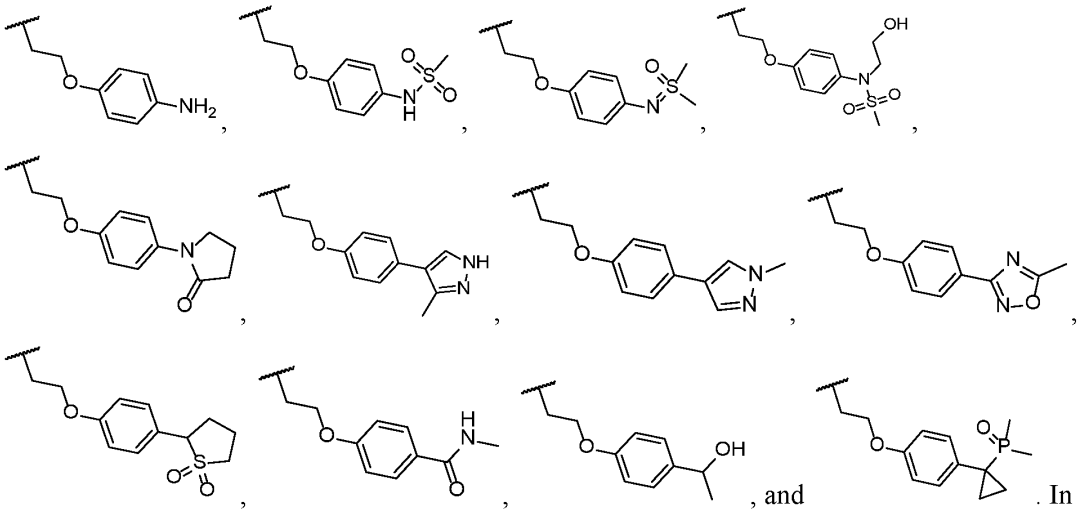
[0157] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a bi-substituted phenyl with one group bound at the para position relative to the phenyl's attachment to L^2. In some embodiments, the bi-substituted phenyl is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , ,  , .



. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

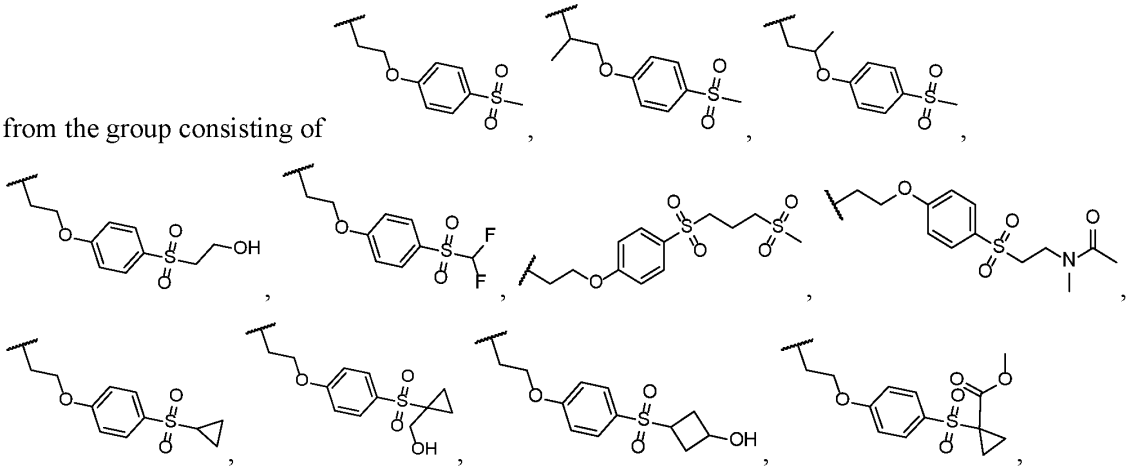
[0158] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a bi-substituted phenyl with one group bound at the para position relative to the phenyl's attachment to L^2. In some embodiments, the bi-substituted phenyl is selected

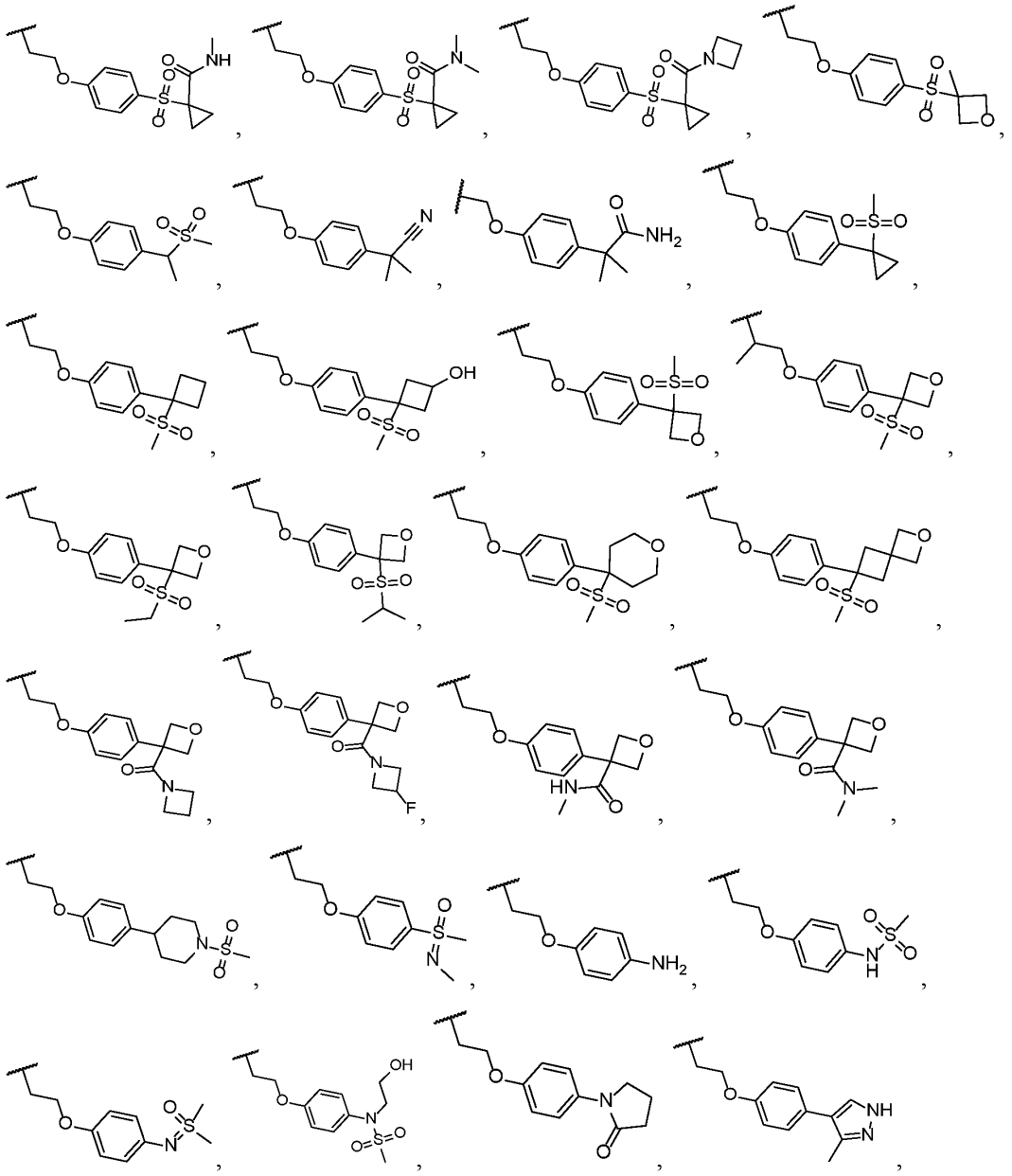
from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , ,  , .

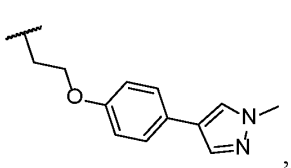
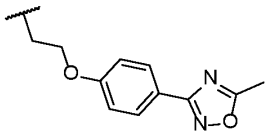
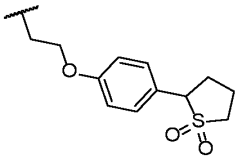
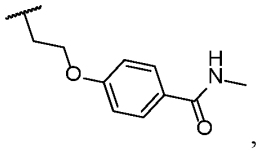
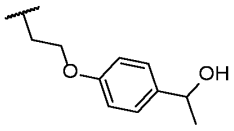
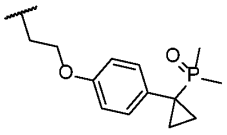


some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

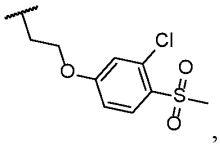
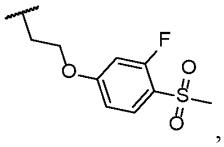
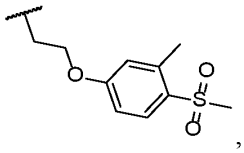
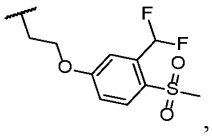
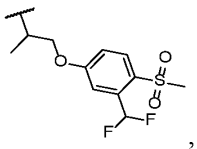
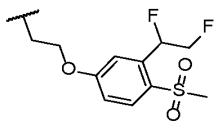
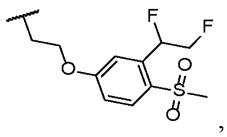
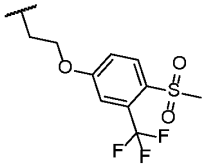
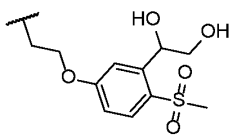
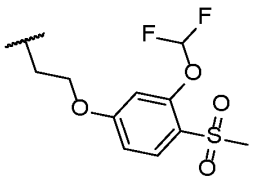
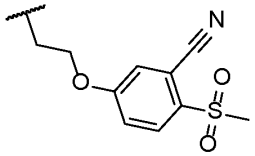
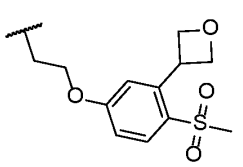
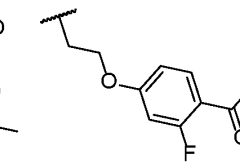
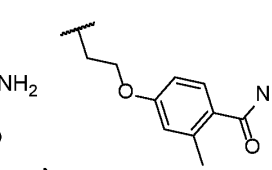
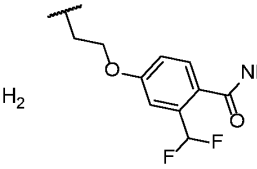
[0159] In some embodiments of a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a bi-substituted phenyl with one group bound at the para position relative to the phenyl's attachment to L^2. In some embodiments, the bi-substituted phenyl is selected from the group consisting of

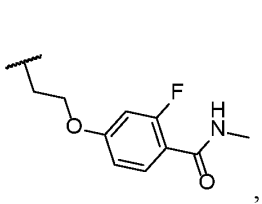
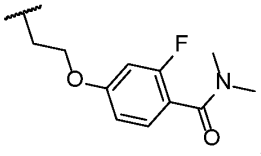
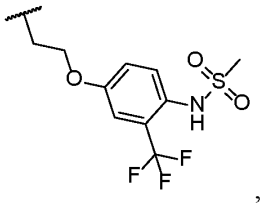
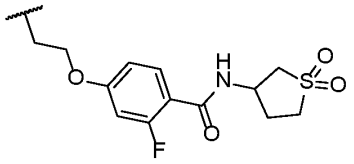
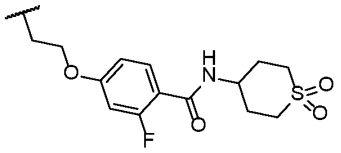
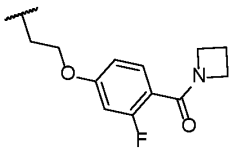
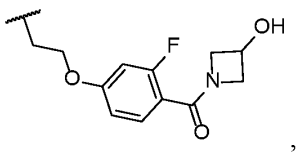
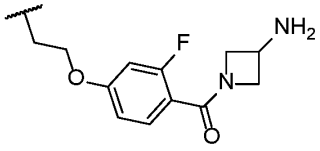
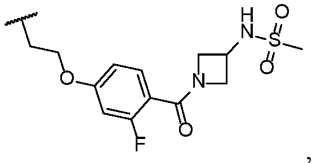
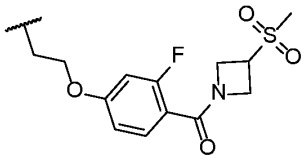
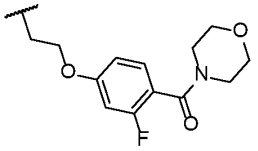
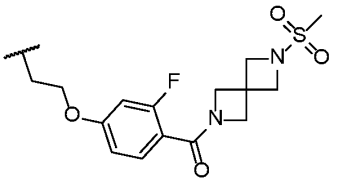
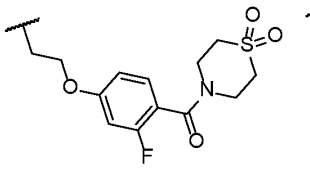
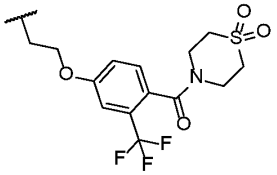
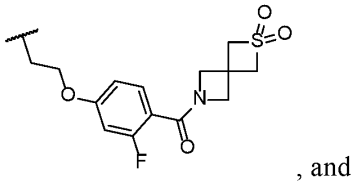
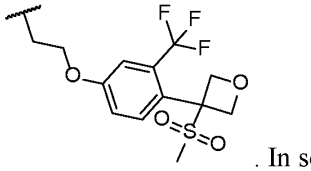
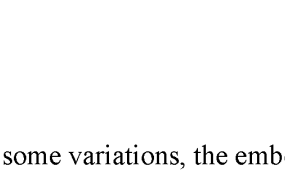
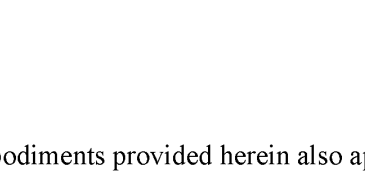
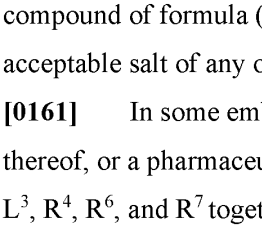










, and .

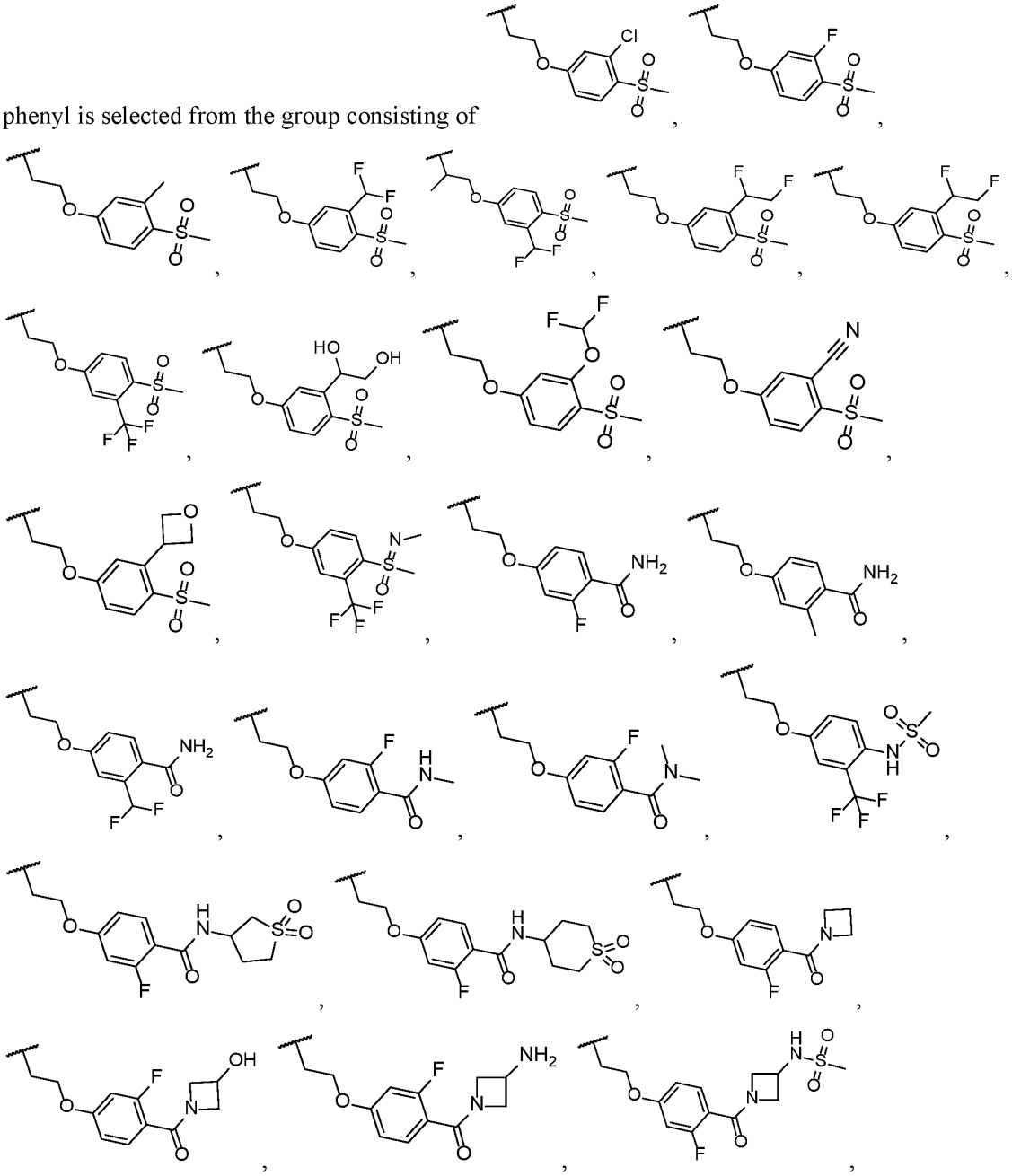
[0160] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a tri-substituted phenyl with two groups bound at a meta, and the para positions relative to the phenyl's attachment to L^2. In some embodiments, the tri-substituted phenyl is selected from the group consisting of

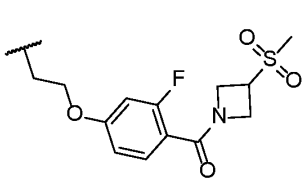
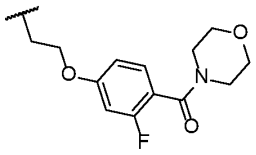
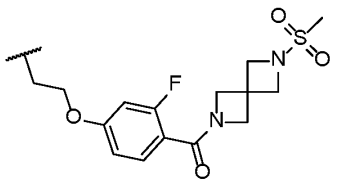
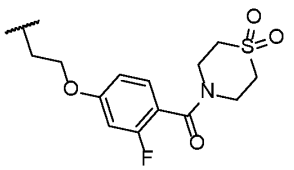
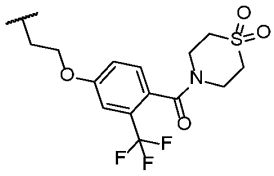
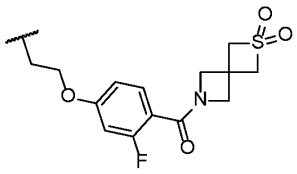
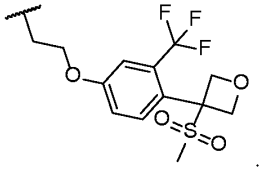
















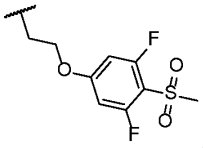
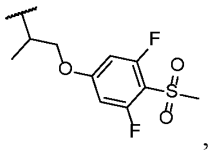
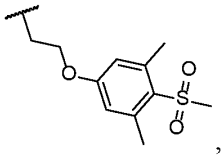
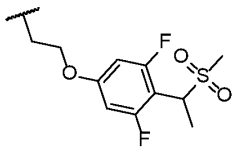
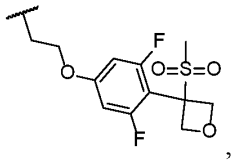
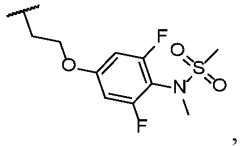
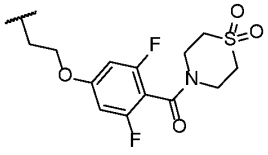

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

, and

. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

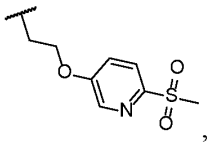
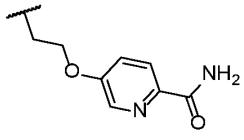
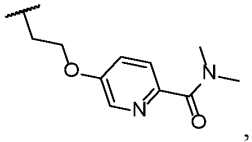
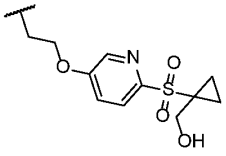
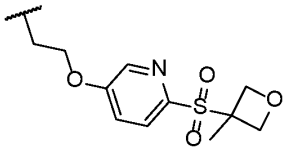
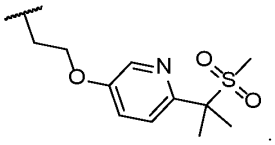
[0161] In some embodiments of a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a tri-substituted phenyl with two groups bound at a meta, and the

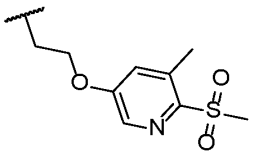
para positions relative to the phenyl's attachment to L^2. In some embodiments, the tri-substituted phenyl is selected from the group consisting of



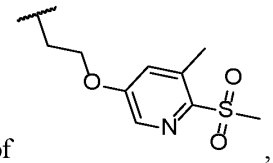
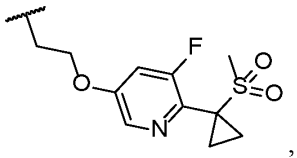
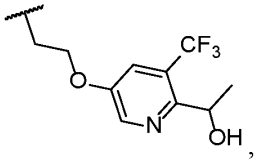
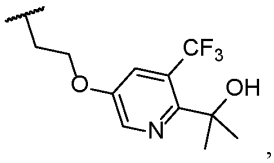
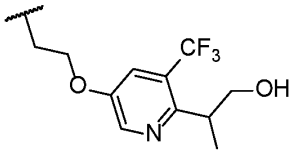
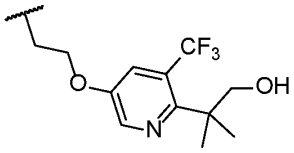
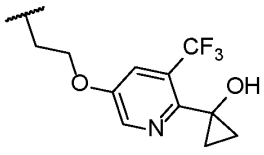
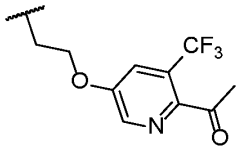

,

,

,

,

,

, and

.

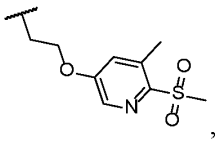
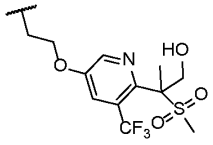
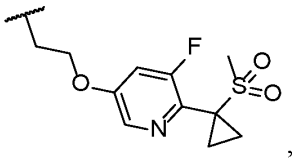
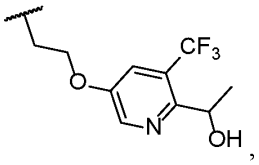
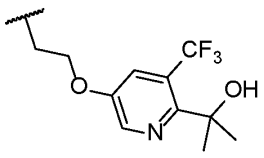
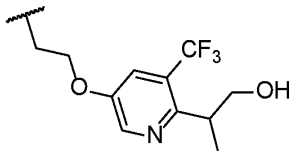
[0162] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a tetra-substituted phenyl with three groups bound at the meta, and para positions relative to the phenyl's attachment to L^2. In some embodiments, the tetra-substituted phenyl is selected from the group consisting of

,

,

,

,

,

, and

. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

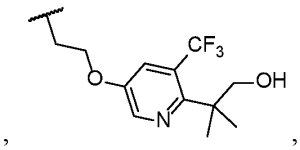
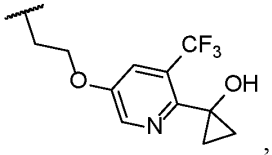
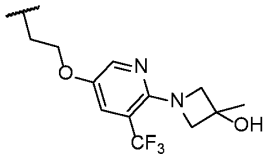
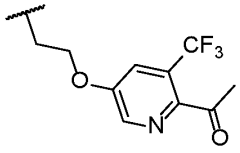
[0163] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a bi-substituted pyridine with one group bound at the para position relative to the pyridine's attachment to L^2. In some embodiments, the bi-substituted pyridine is selected from the group consisting of  ,  ,  ,  ,  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

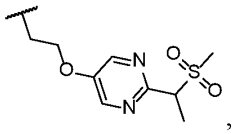
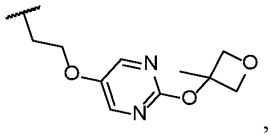
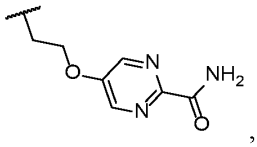
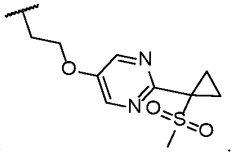
[0164] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a tri-substituted pyridine with two groups bound at the meta, and para positions relative to the pyridine's attachment to L^2. In some embodiments, the tri-substituted pyridine is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

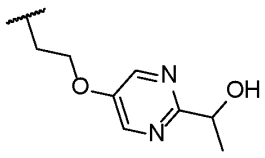
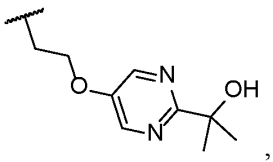
[0165] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a tri-substituted pyridine with two groups bound at the meta, and para positions relative to the pyridine's attachment to L^2. In some embodiments, the tri-substituted

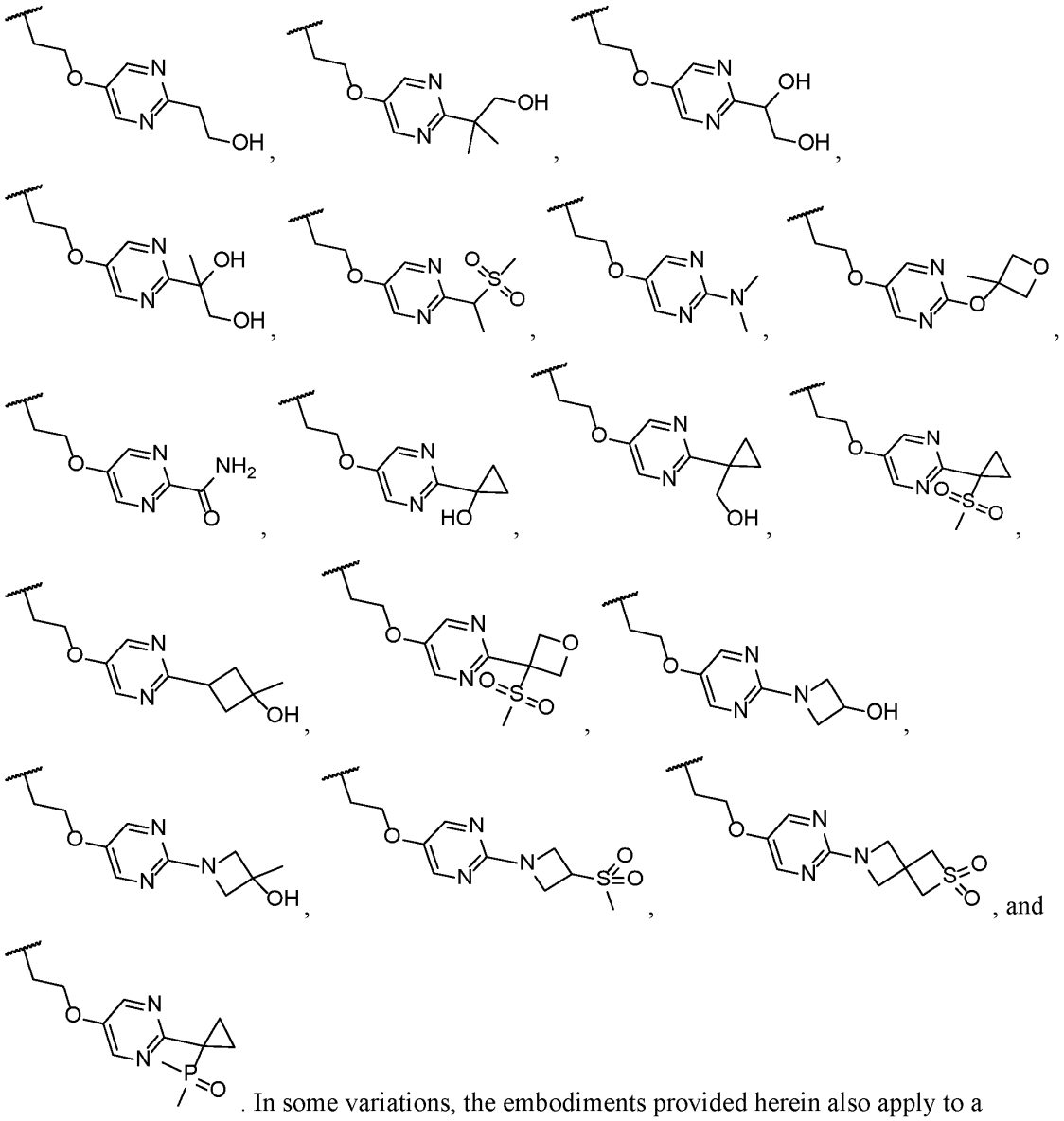
pyridine is selected from the group consisting of  ,  ,  ,  ,  ,  ,  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0166] In some embodiments of a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a tri-substituted pyridine with two groups bound at the meta, and para positions relative to the pyridine's attachment to L^2. In some embodiments, the tri-substituted pyridine is selected from the group consisting of  ,  ,  ,  ,  , 




, and

.

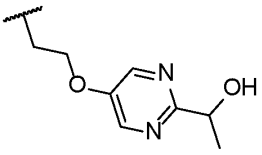
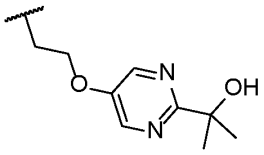
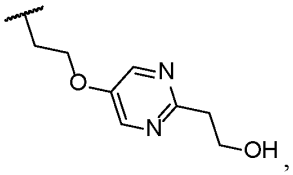
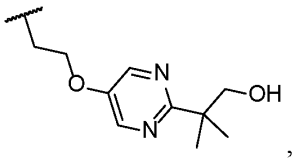
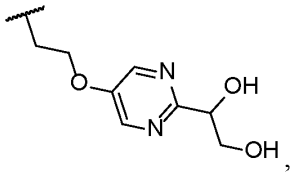
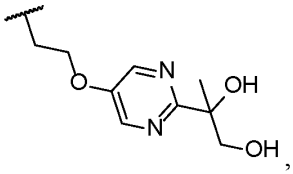
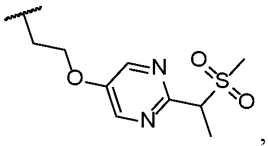
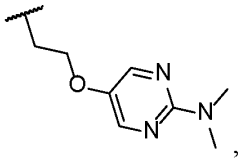
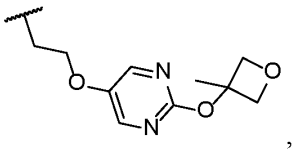
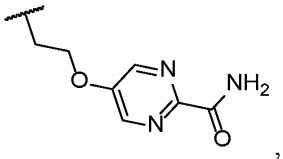
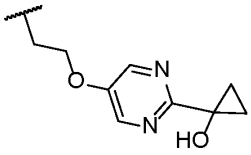
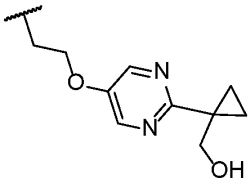
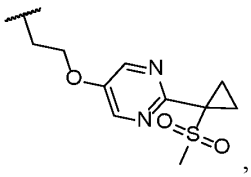
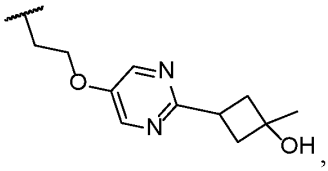
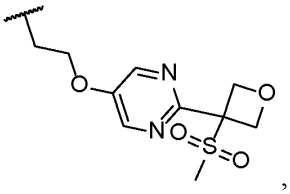
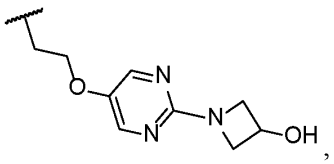
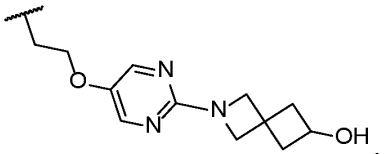
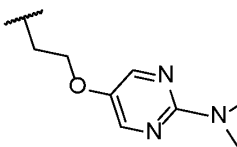
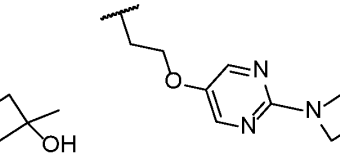
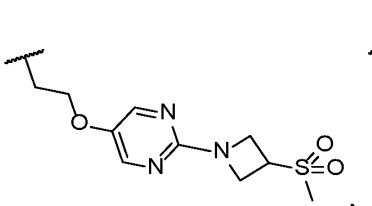
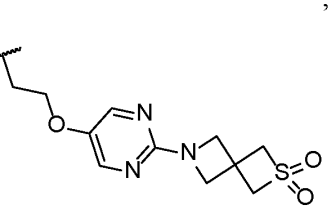
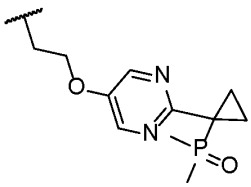
[0167] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a bi-substituted pyrimidine with two groups bound at the para position relative to the pyrimidine's attachment to L^2. In some embodiments, the bi-substituted pyrimidine is selected from the group consisting of

,

,

, and

. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

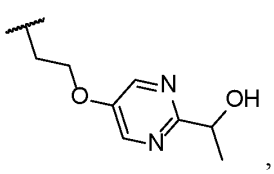
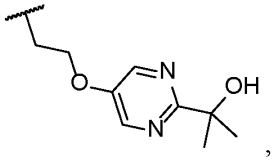
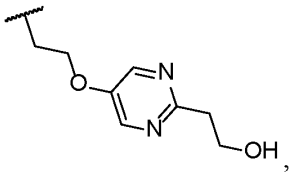
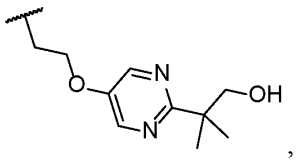
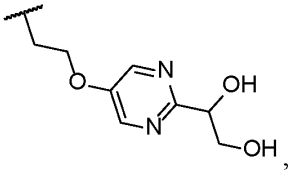
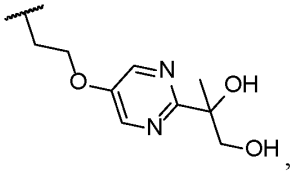
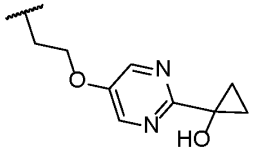
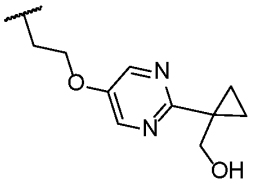
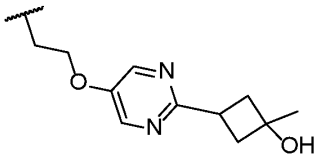
[0168] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a bi-substituted pyrimidine with two groups bound at the para position relative to the pyrimidine's attachment to L^2. In some embodiments, the bi-substituted pyrimidine is selected from the group consisting of

,

,



. In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

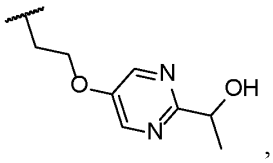
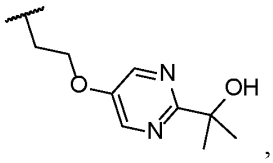
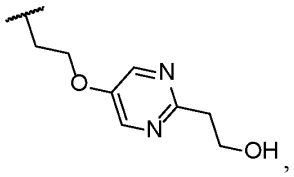
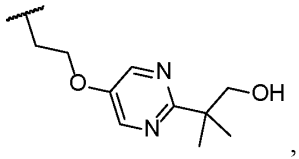
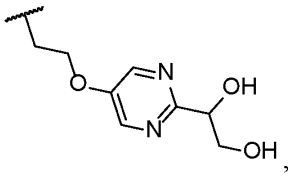
[0169] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a bi-substituted pyrimidine with two groups bound at the para

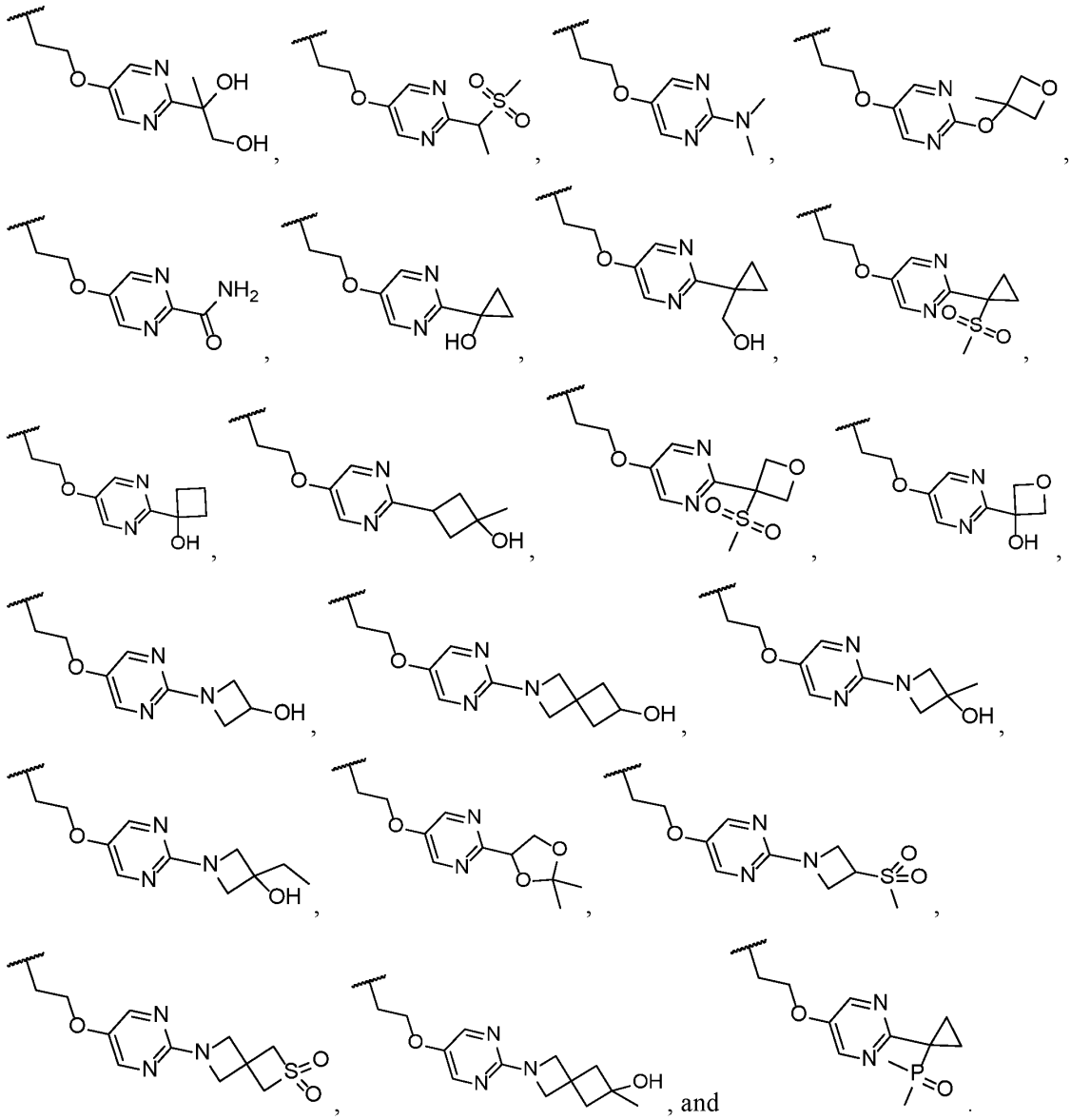
position relative to the pyrimidine's attachment to L^2. In some embodiments, the bi-substituted pyrimidine is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In some embodiments, the bi-substituted pyrimidine is selected from the group consisting of

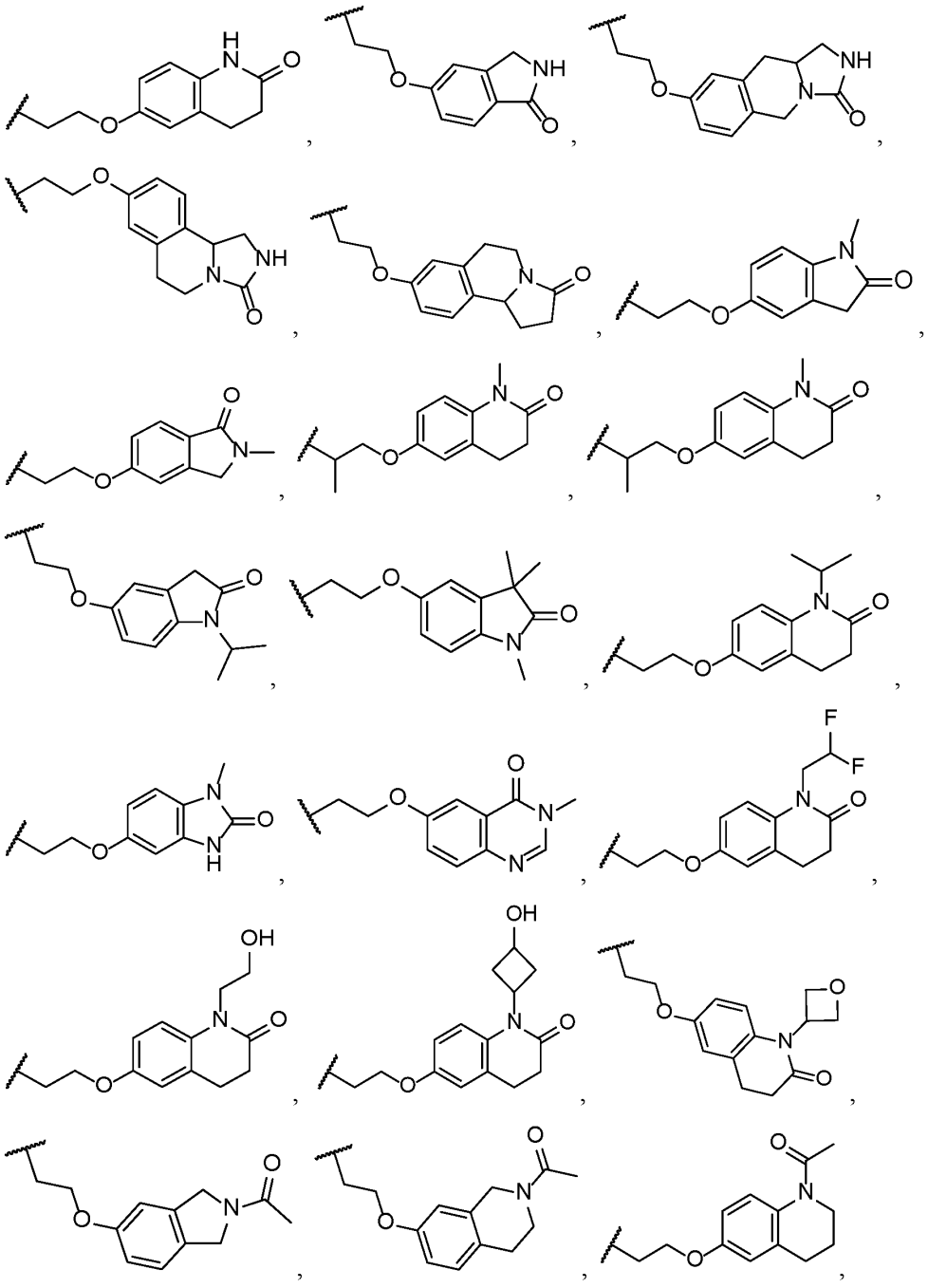
variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

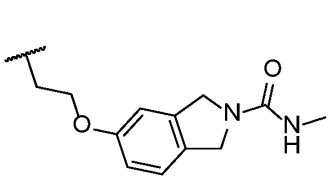
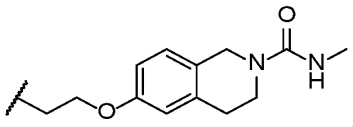
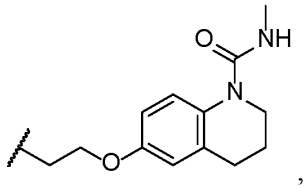
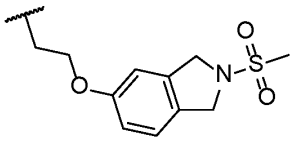
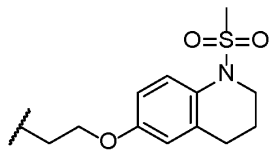
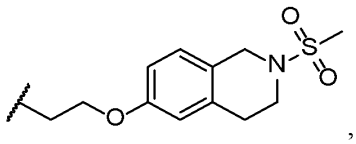
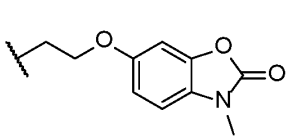
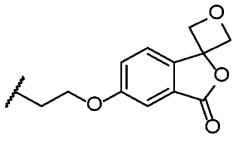
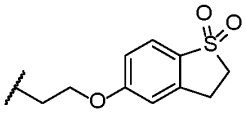
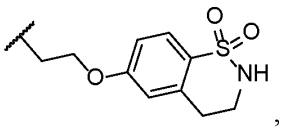
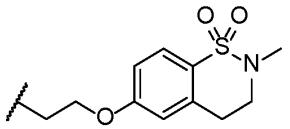
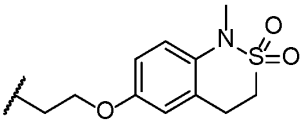
[0170] In some embodiments of a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a bi-substituted pyrimidine with two groups bound at the para position relative to the pyrimidine's attachment to L^2. In some embodiments, the bi-substituted pyrimidine is selected from the group consisting of



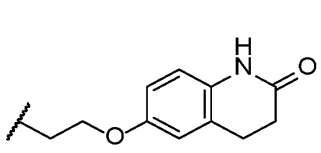
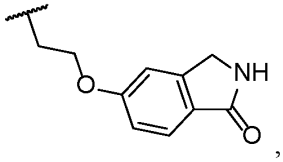
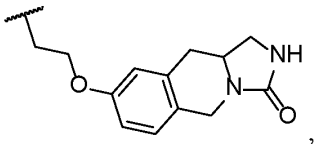
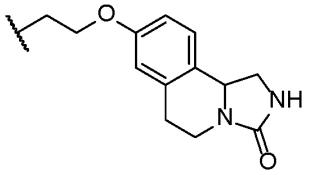
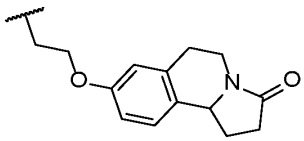
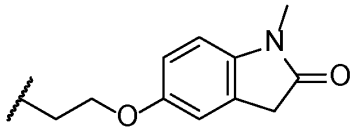
[0171] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a heterocycle selected from the group consisting of

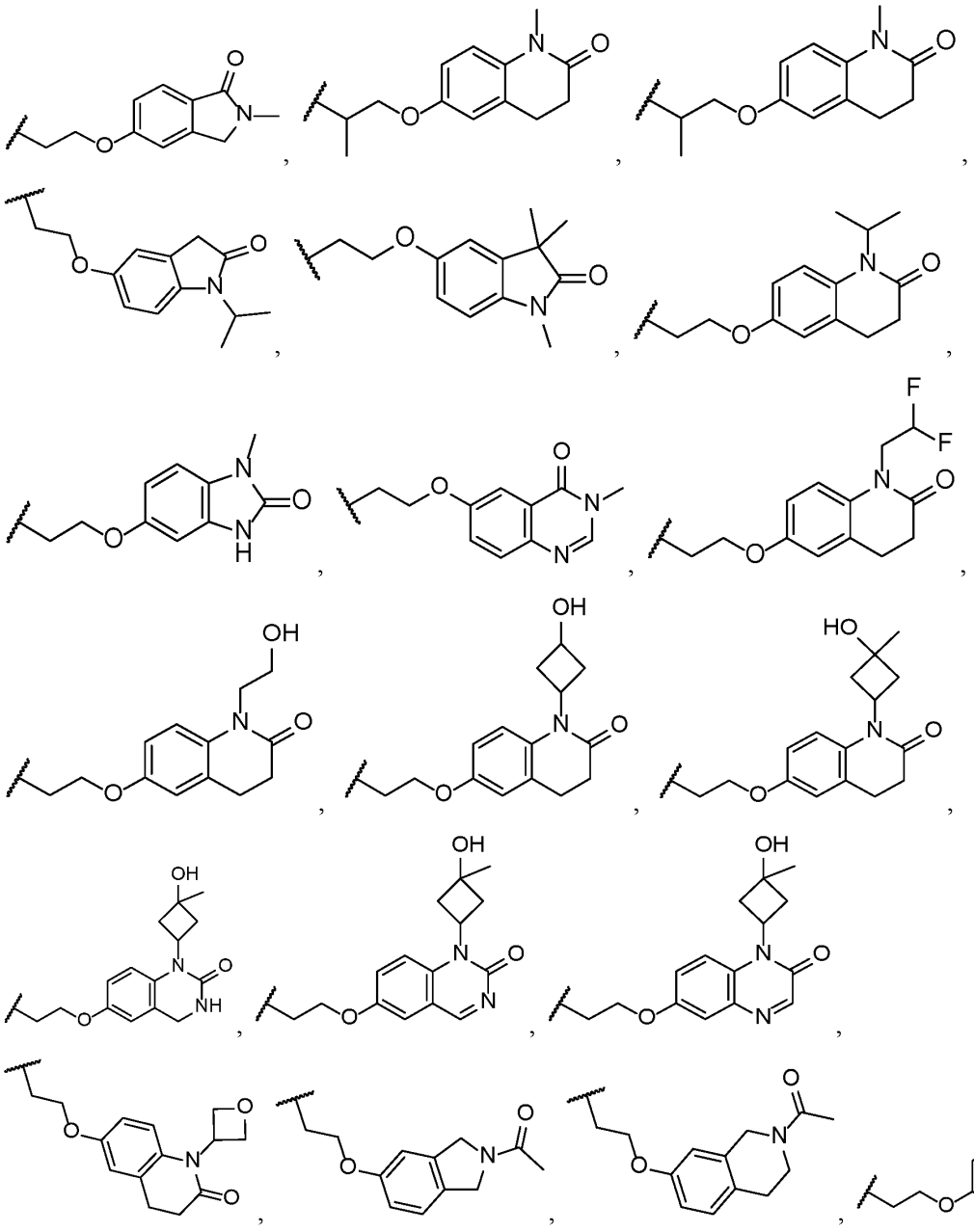


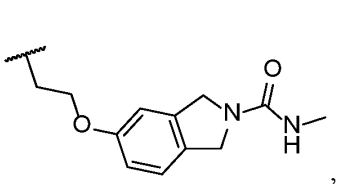
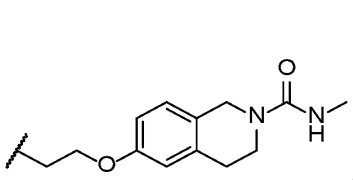
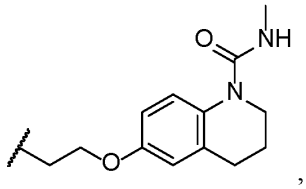
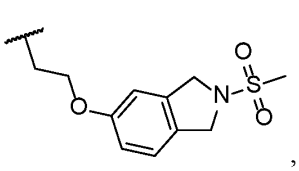
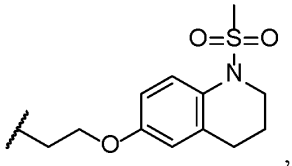
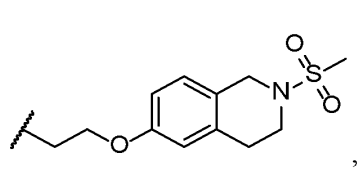
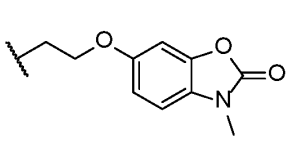
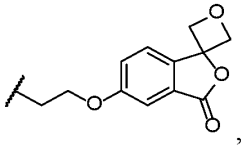
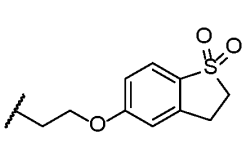
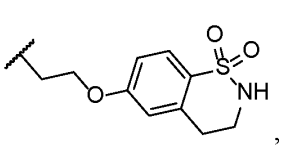
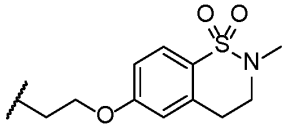
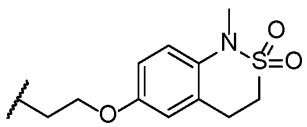













, and . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

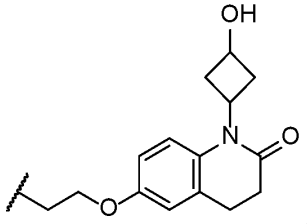
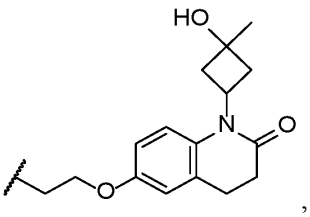
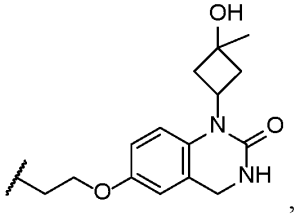
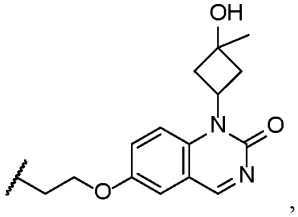
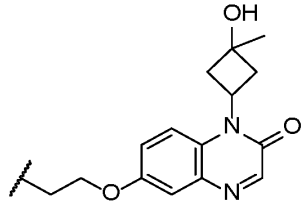
[0172] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a heterocycle selected from the group consisting of



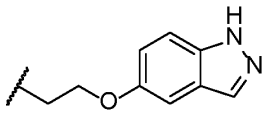
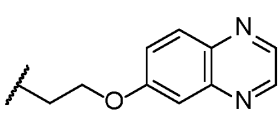
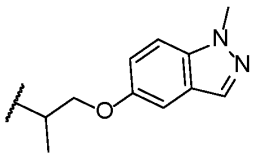
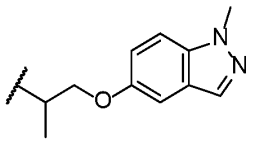
, and . In some embodiments, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a heterocycle selected from the group consisting of

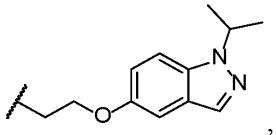
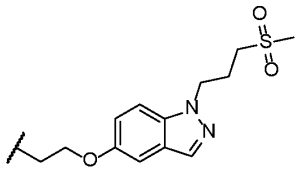
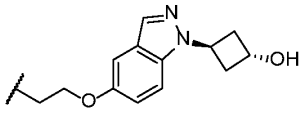






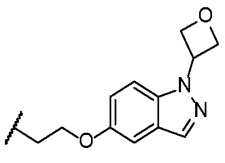
, and . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0173] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing

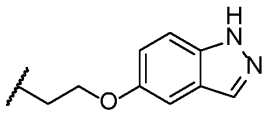
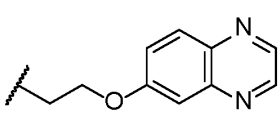
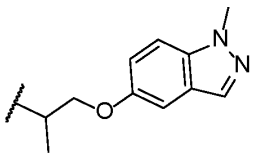
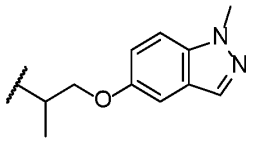
L^3, R^4, R^6, and R^7 together form a heteroaryl selected from the group consisting of

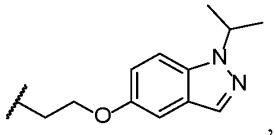
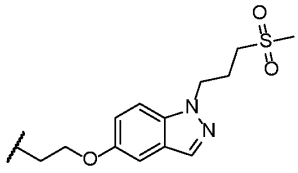
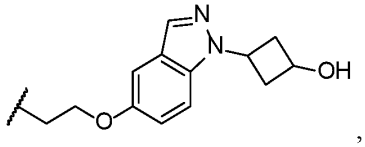
 ,  ,  ,  ,

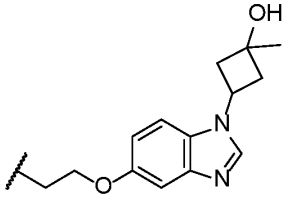
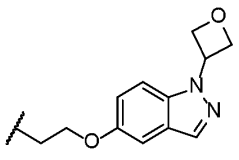
 ,  ,  , and

 . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

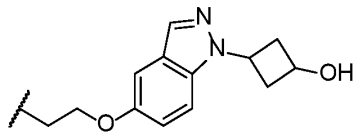
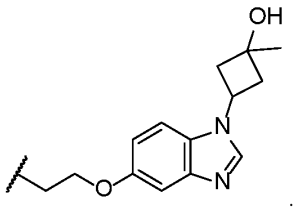
[0174] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a heteroaryl selected from the group consisting of

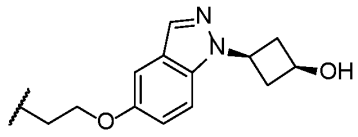
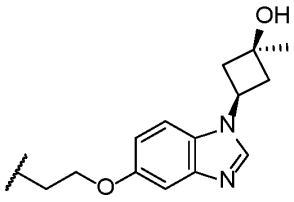
 ,  ,  ,  ,

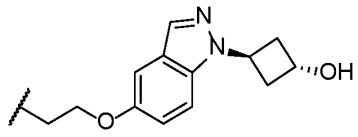
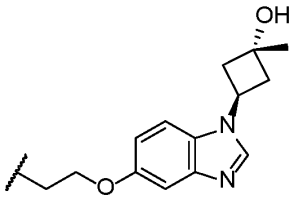
 ,  ,  ,

 , and  . In some embodiments, L^1, L^2, and the ring

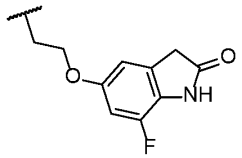
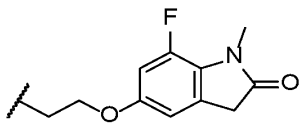
bearing L^3, R^4, R^6, and R^7 together form a heteroaryl selected from the group consisting of

 and  . In some embodiments, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a heteroaryl selected from the group consisting of

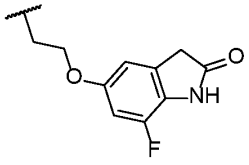
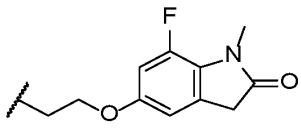
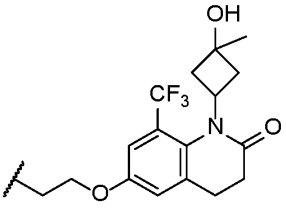
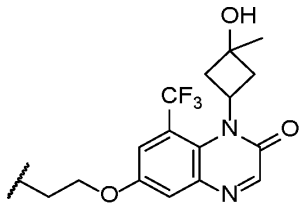
 and  . In some embodiments, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a heteroaryl selected from the group consisting of

 and  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

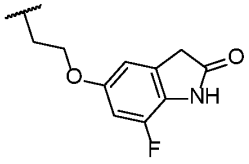
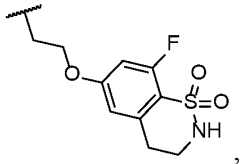
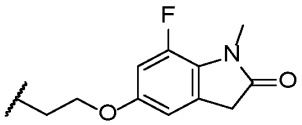
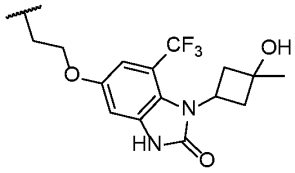
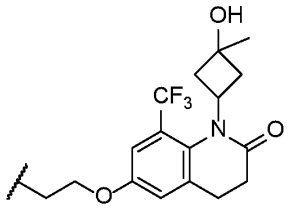
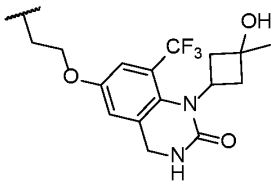
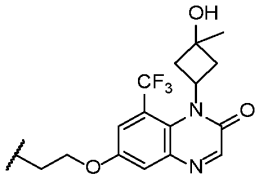
[0175] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a heterocycle selected from the group consisting of

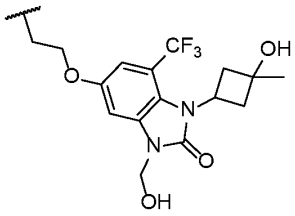
 , and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0176] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a heterocycle selected from the group consisting of

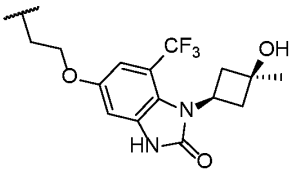

,

,

, and

. In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0177] In some embodiments of a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a heterocycle selected from the group consisting of

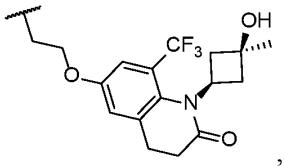

,

,

,

,

,

,

, and



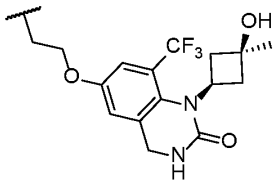
. In some embodiments, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a heterocycle selected from the group consisting of



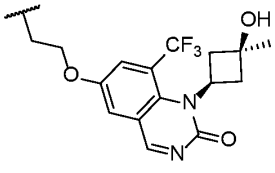
,



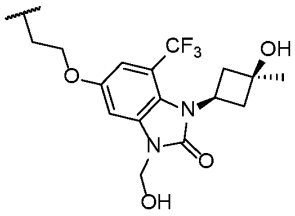
,



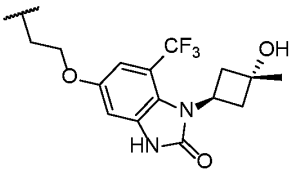
,



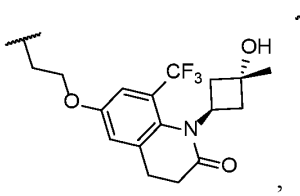
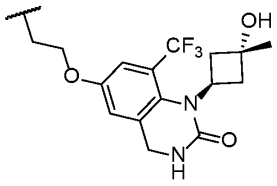
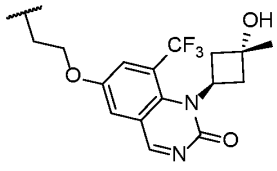
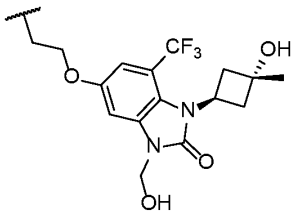
, and

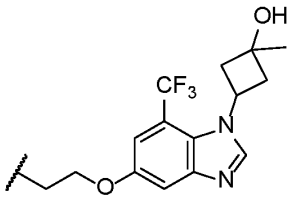
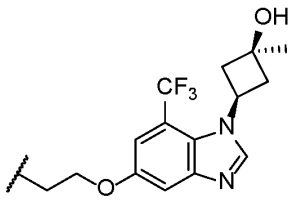
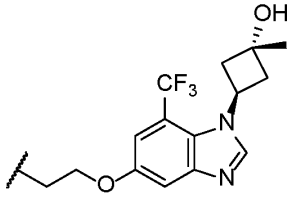


. In some embodiments, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a heterocycle selected from the group consisting of

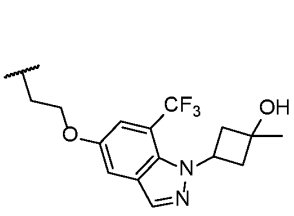
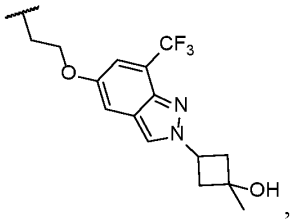
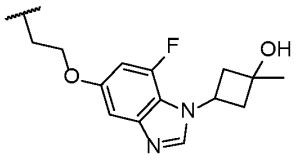
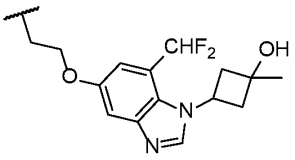
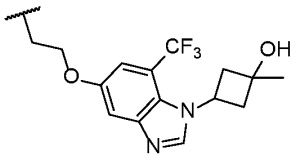
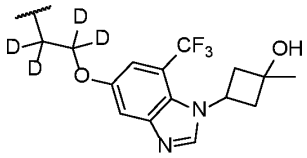
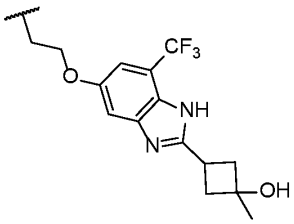
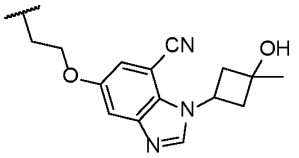
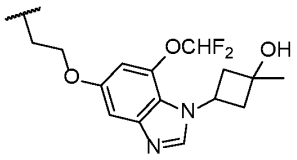
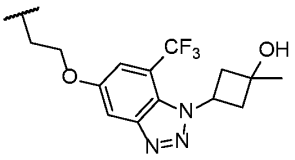
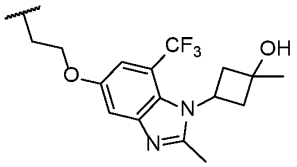
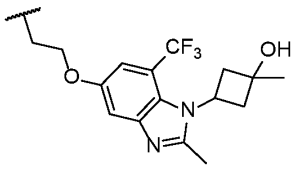
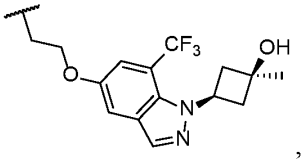
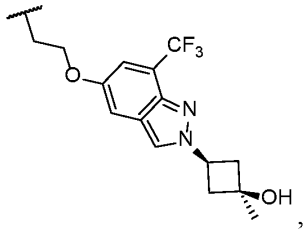
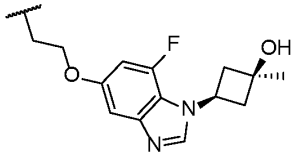


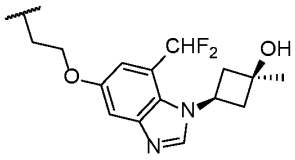
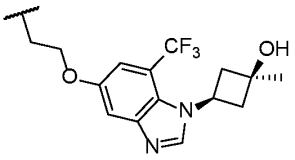
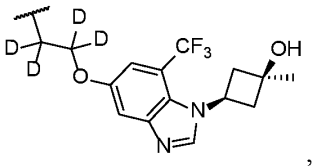
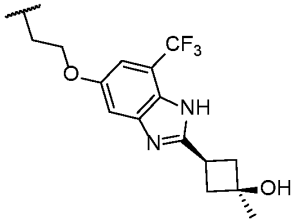
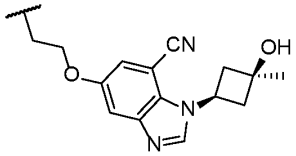
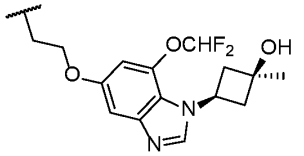
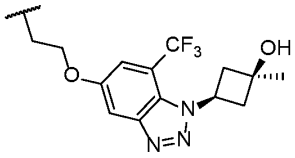
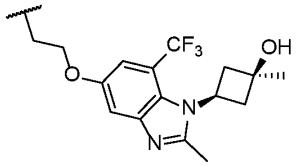
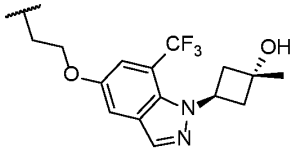
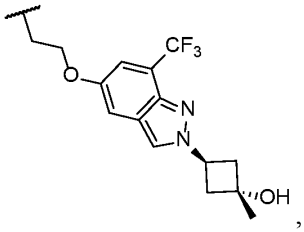
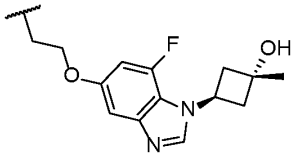
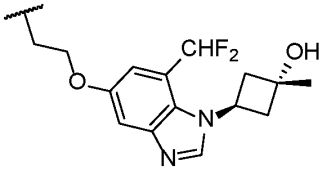
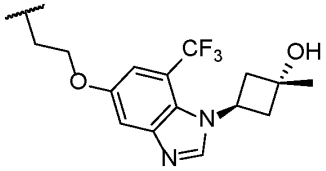
,

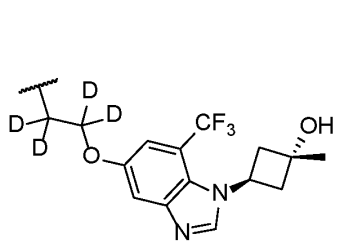
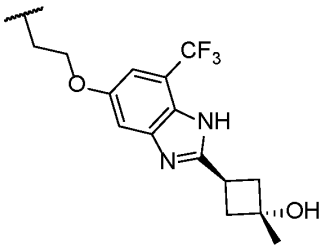
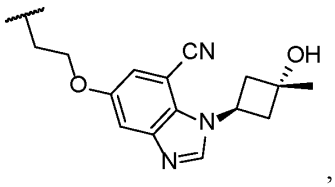
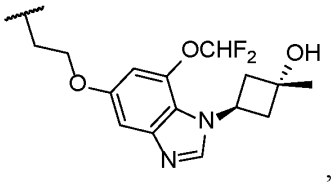
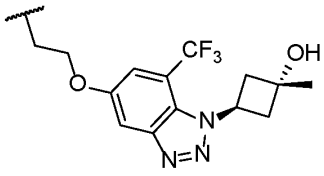
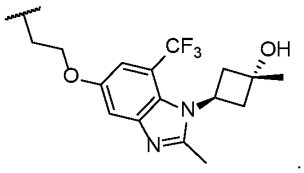



, and


[0178] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form  . In some embodiments, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form  . In some embodiments, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

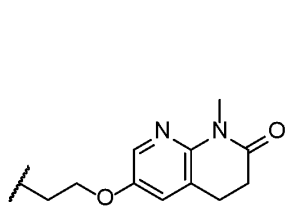
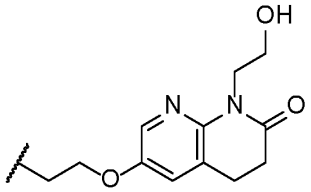
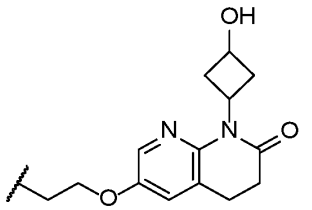
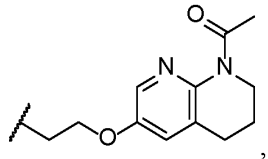
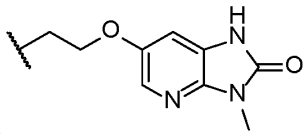
[0179] In some embodiments of a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing

L^3, R^4, R^6, and R^7 together form  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  . In some embodiments, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form  ,  ,  ,









, or . In some embodiments, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form 





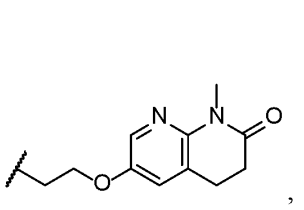
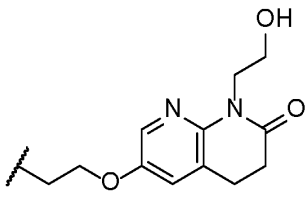
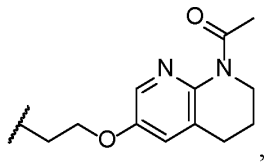
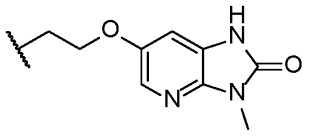
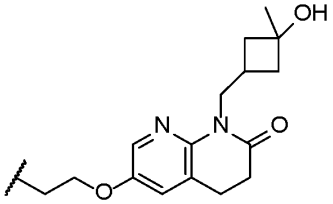
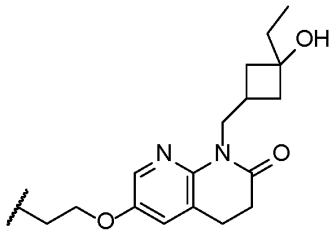
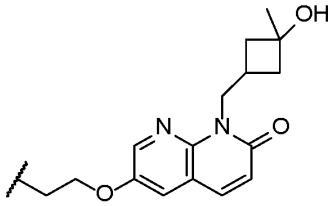
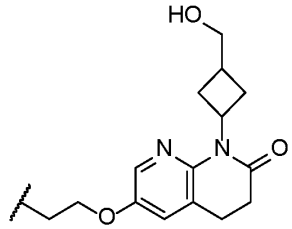
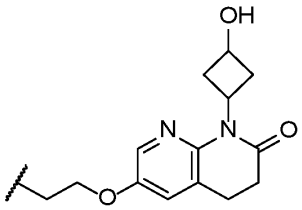
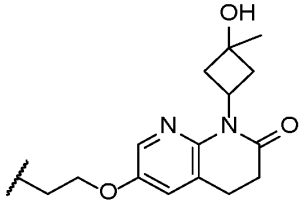
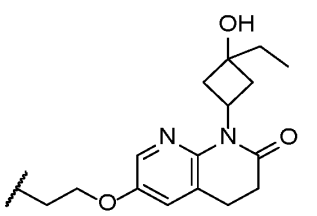
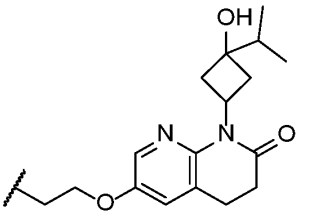
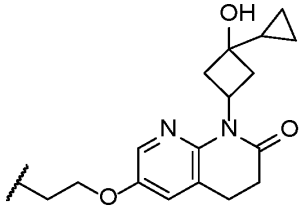
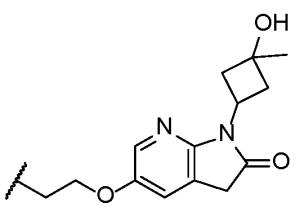
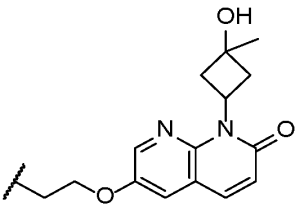







[0180] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a heterocycle selected from the group consisting of

. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

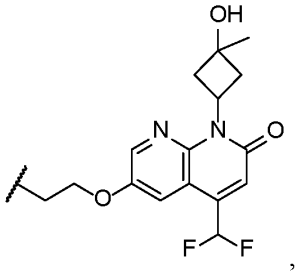
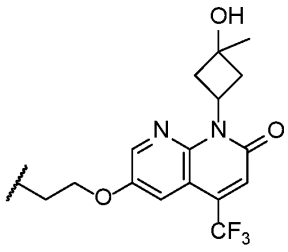
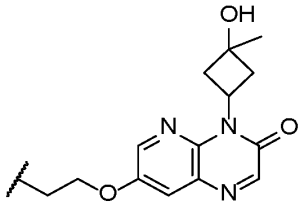
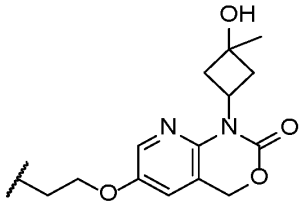
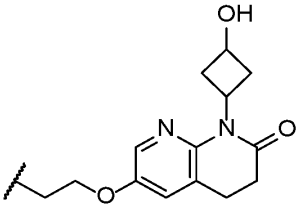
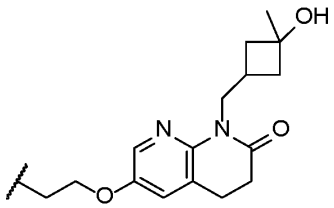
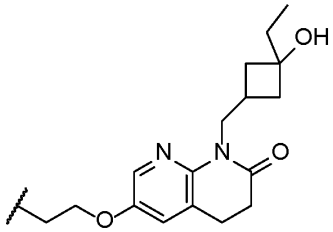
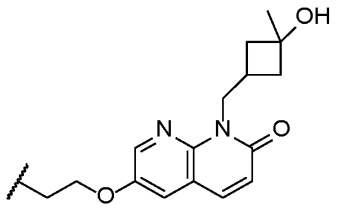
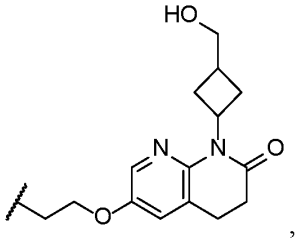
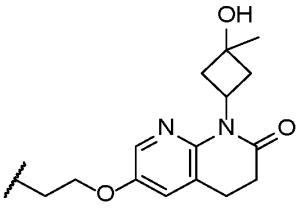
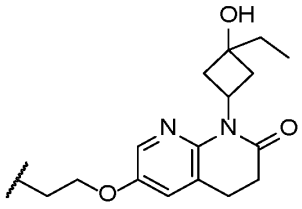
[0181] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a heterocycle selected from the group consisting of

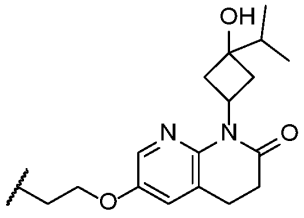
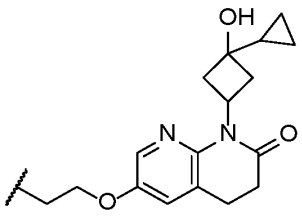
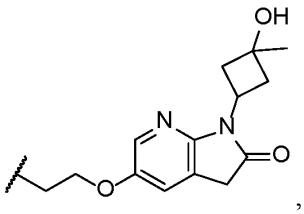
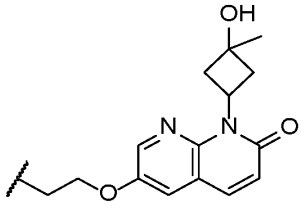
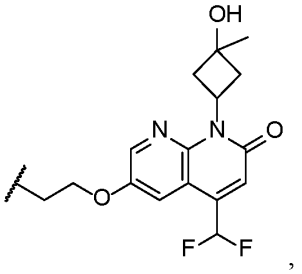
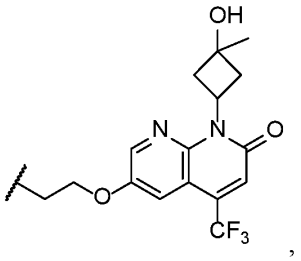
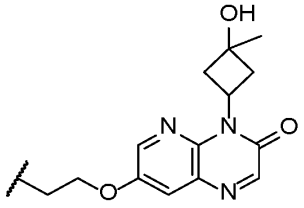
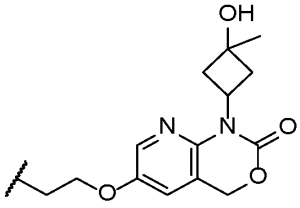

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

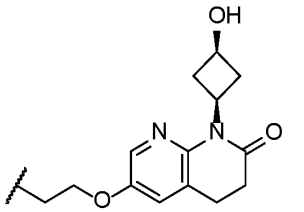
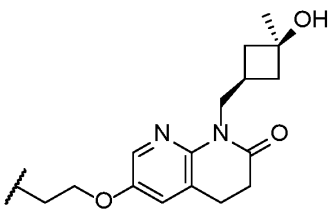
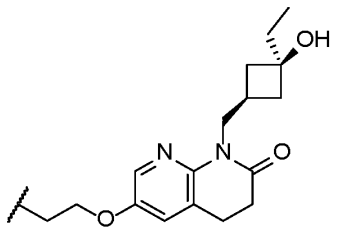
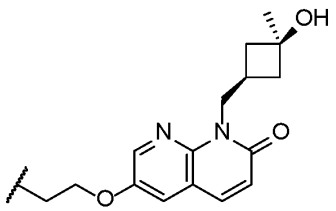
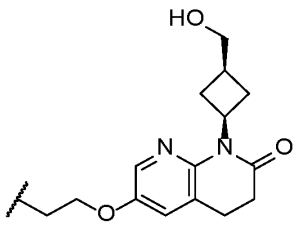
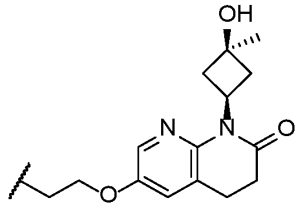
,

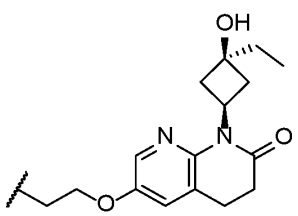
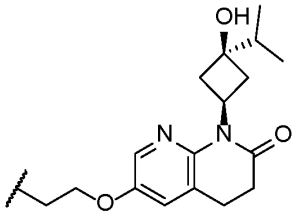
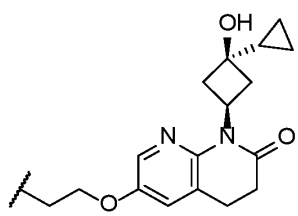
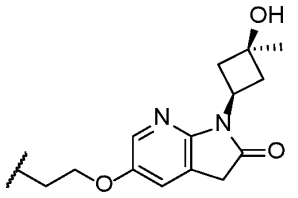
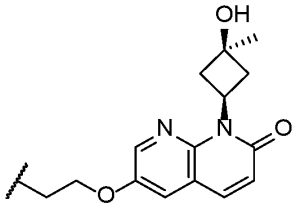
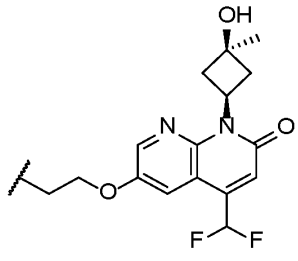
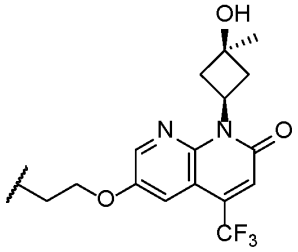
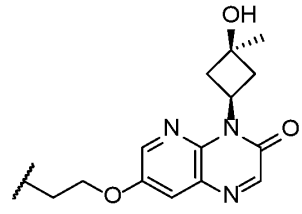
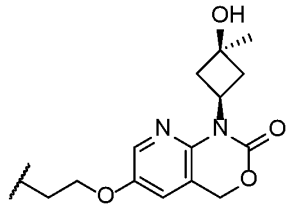
,

,

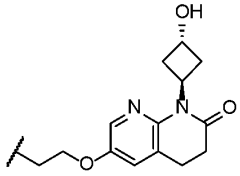
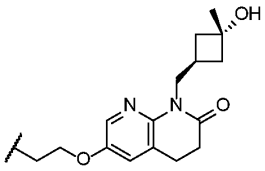
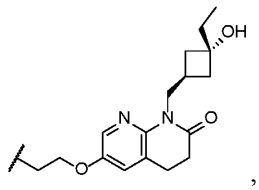
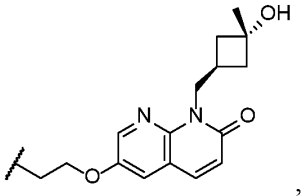
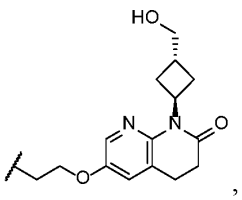
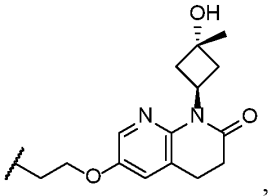
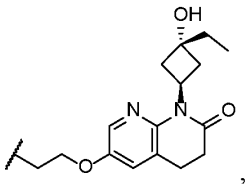
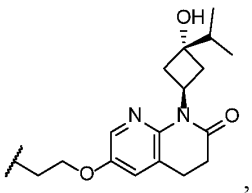
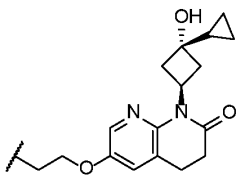
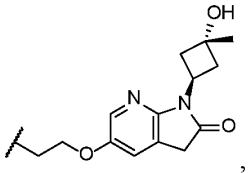
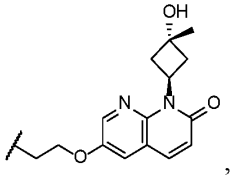
 ,  ,  , and  . In some embodiments, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a heterocycle selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,

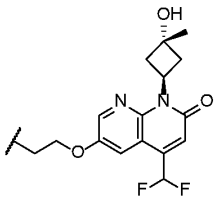
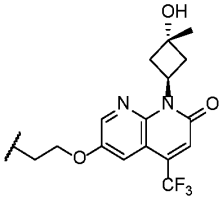
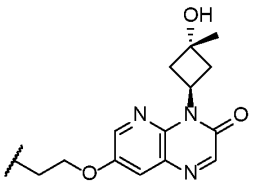
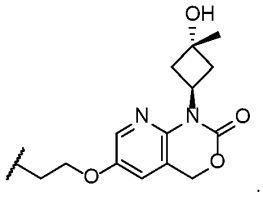

,

,

,

,

,

,

, and

. In some embodiments, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a heterocycle selected from the group consisting of


,

,

,

,

,

,

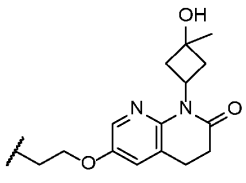
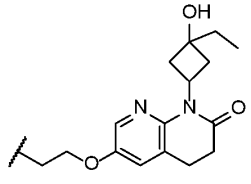
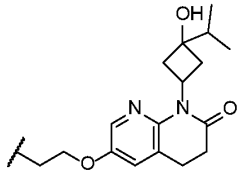
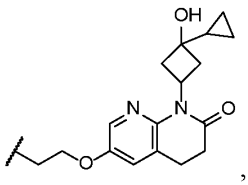
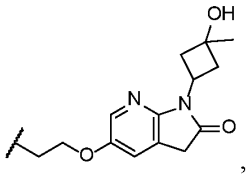
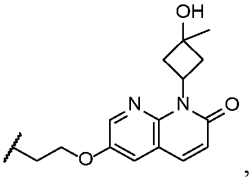
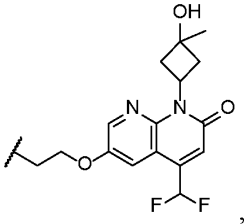
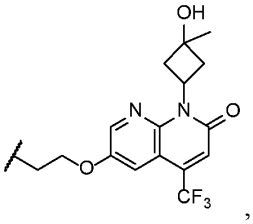
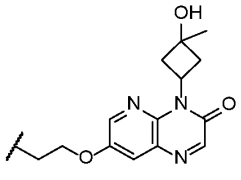
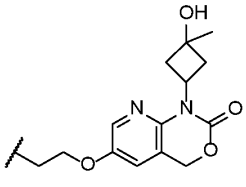










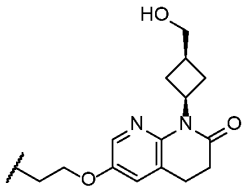
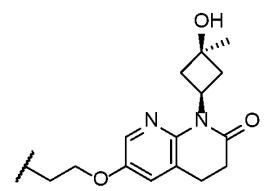
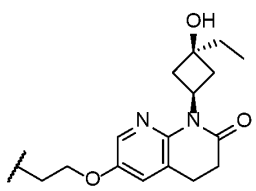
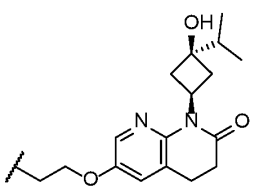
. In some embodiments, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a heterocycle selected from the group consisting of

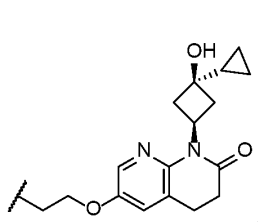
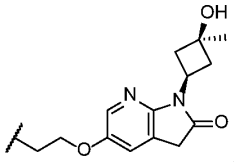
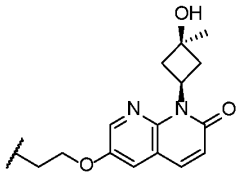
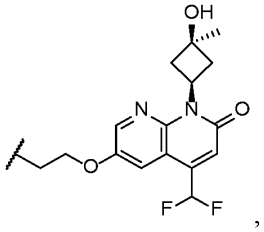
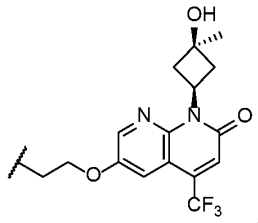
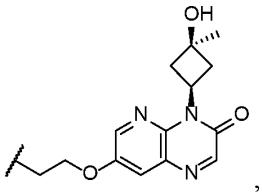
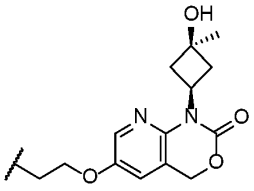















, and  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

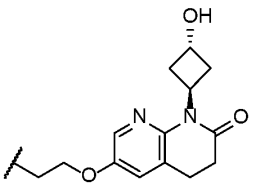
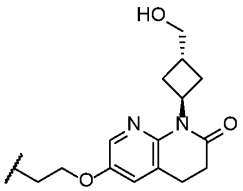
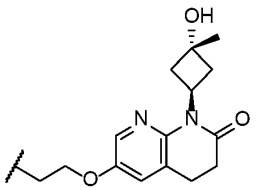
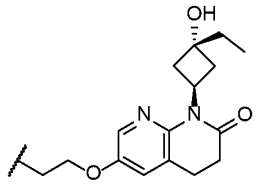
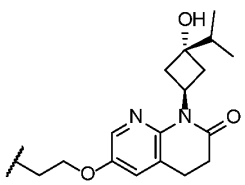
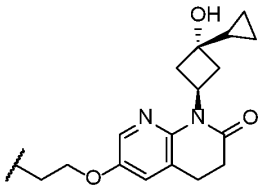
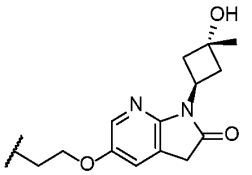
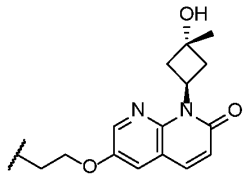
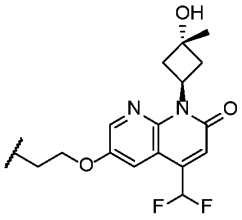
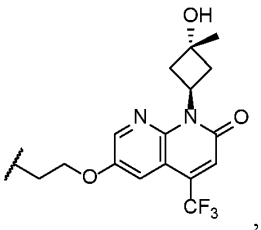
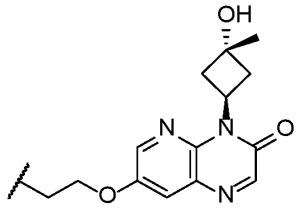
[0182] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a heterocycle selected from the group consisting of










, and  . In some embodiments, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a heterocycle selected from the group consisting of

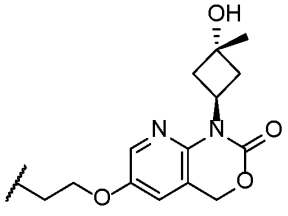





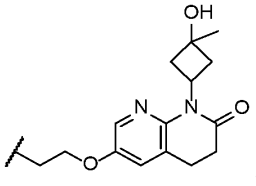
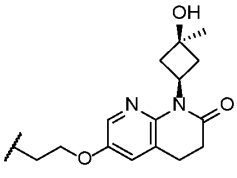
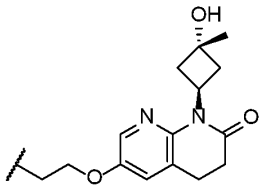
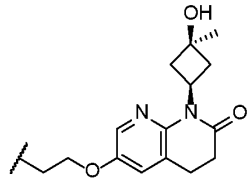
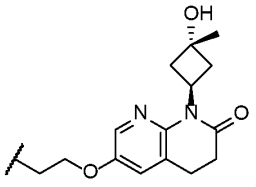
. In some embodiments, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a heterocycle selected from the group consisting of

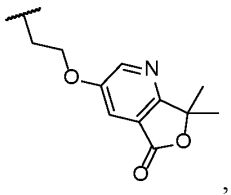












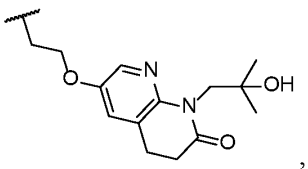
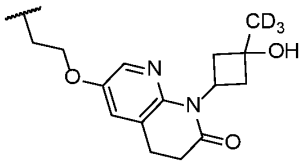
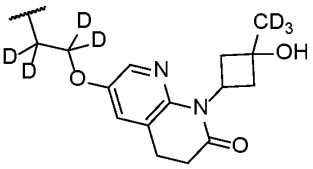
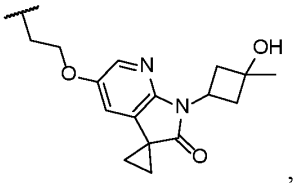
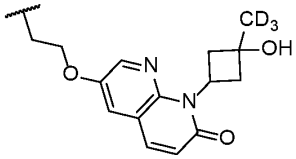
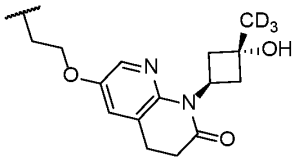
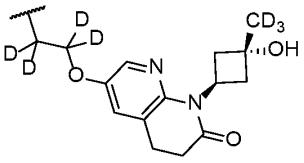
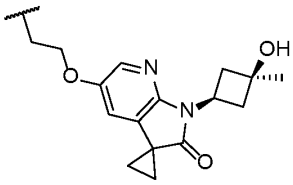
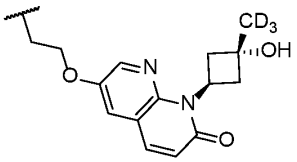
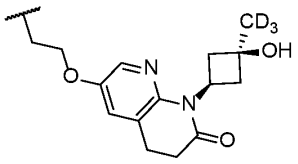
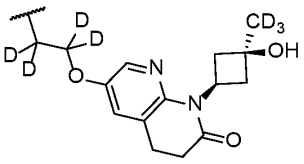
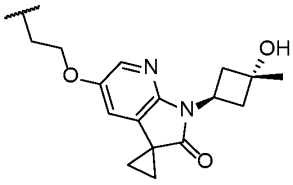
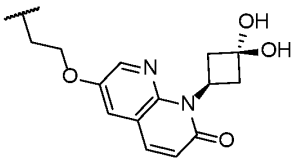
, and



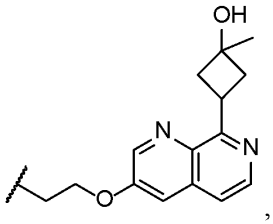
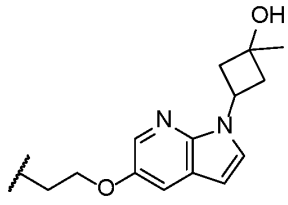
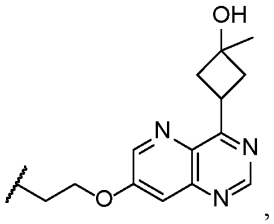
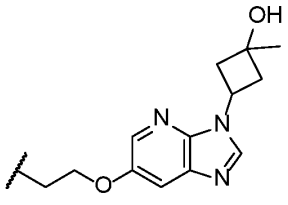
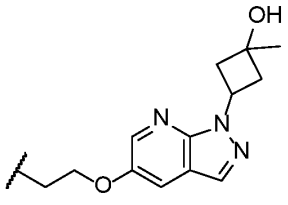
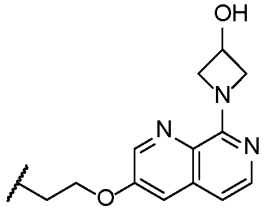
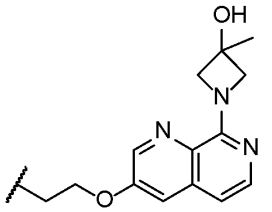
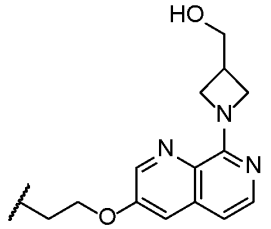
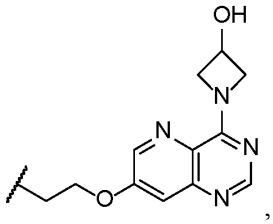
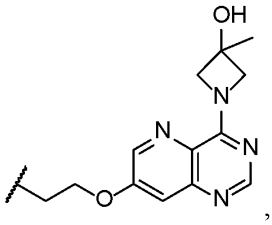
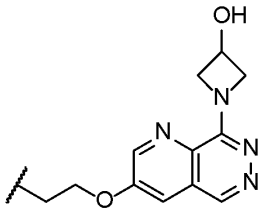
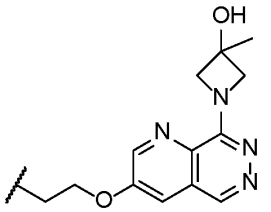
. In some embodiments, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7

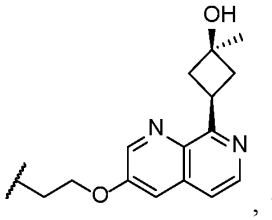
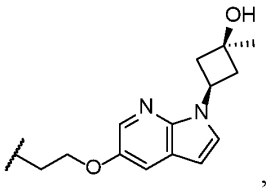
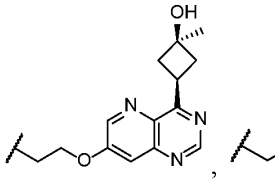
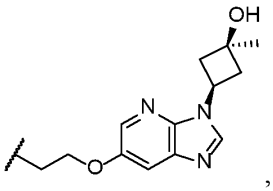
together form  . In some variations, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a heterocycle selected from the group consisting of  and  . In certain variations, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form  . In certain variations, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

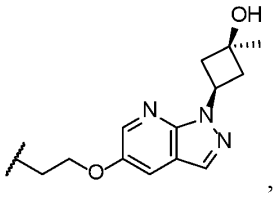
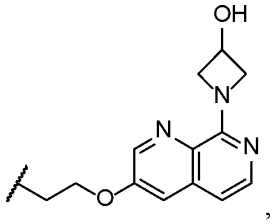
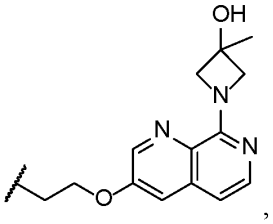
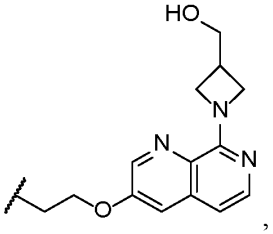
[0183] In some embodiments of a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing L^3, and R^4 together form a heterocycle selected from the group consisting of  ,

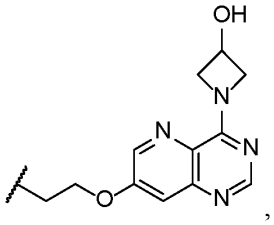
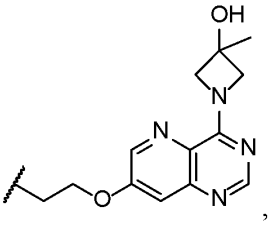
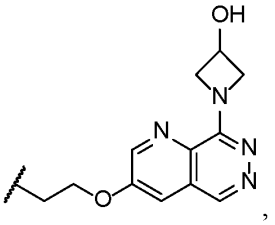

,

,

,

, and

. In certain variations, L^1, L^2, and the ring bearing L^3, and R^4 together form

,

,

, or

. In certain variations, L^1, L^2, and the ring bearing L^3, and R^4 together form

,

,

, or

.

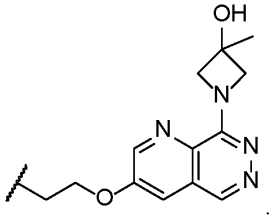
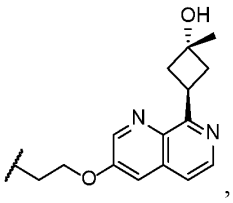
[0184] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a heteroaryl selected from the group consisting of

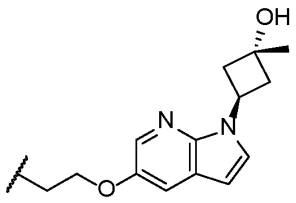
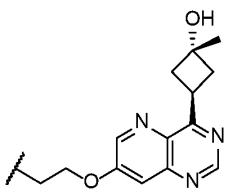
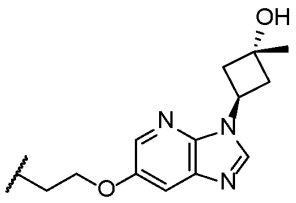

,

,

,

,

,

,

,

,

,

,

, and

. In some embodiments, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a heteroaryl selected from the group consisting of

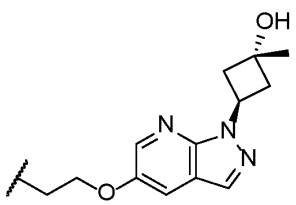
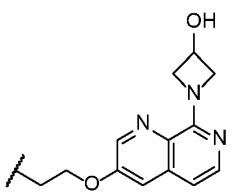
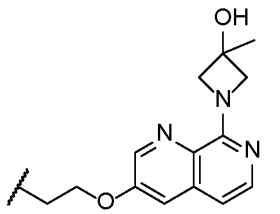
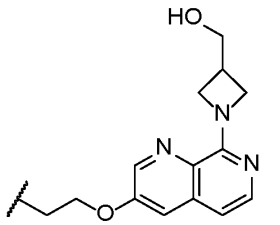

,

,

,

,

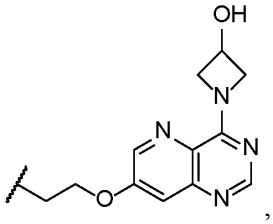
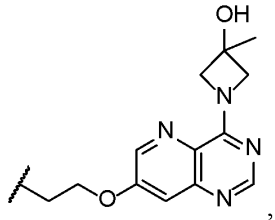
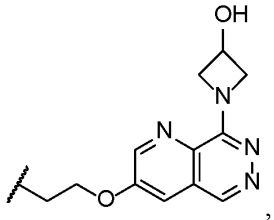
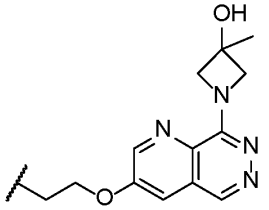
 ,  ,  ,  ,

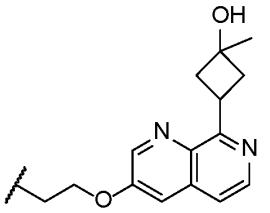
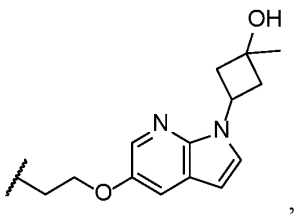
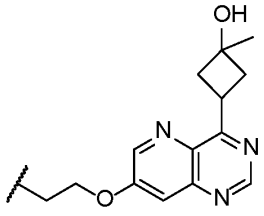
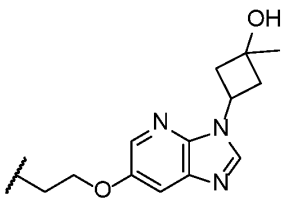
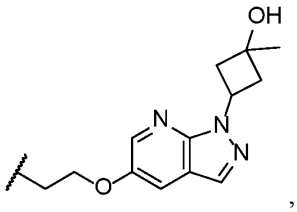
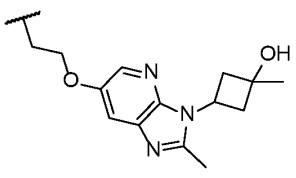
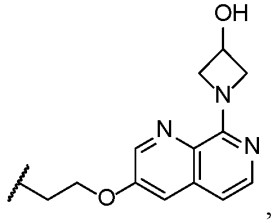
 ,  ,  , and

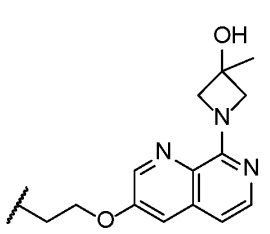
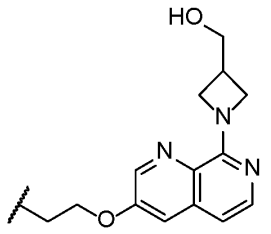
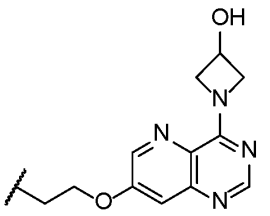
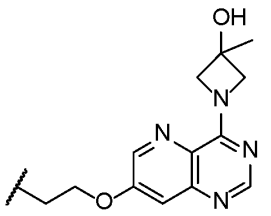
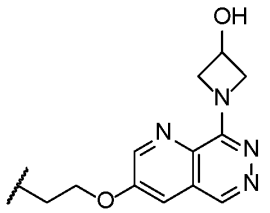
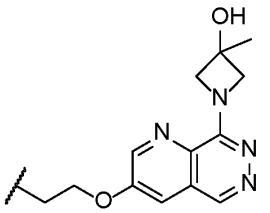
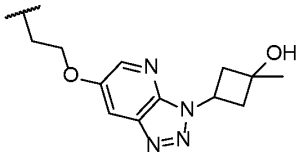
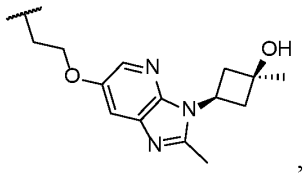
 . In some embodiments, L^1, L^2, and the ring bearing L^3, R^4, R^6, and R^7 together form a heteroaryl selected from the group consisting of  ,

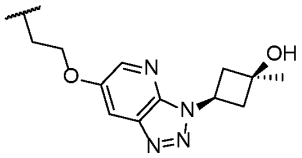
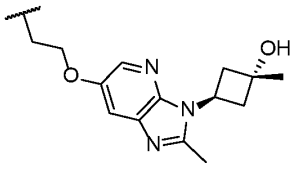
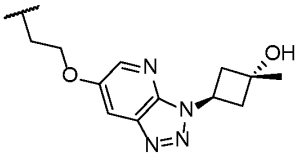
 ,  ,  ,

 ,  ,  ,  ,

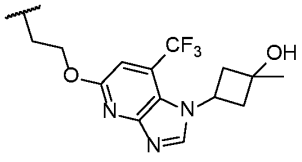
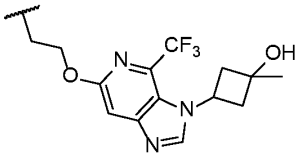



, and

. In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

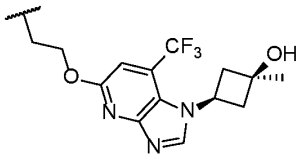
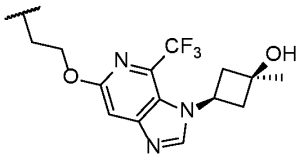
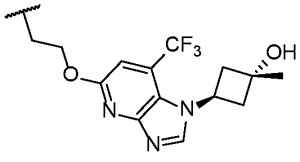
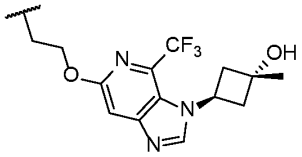
[0185] In some embodiments of a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing R^6, and R^7 together form a heteroaryl selected from the group consisting of

,

,


,

,

,

,

embodiments, L^1, L^2, and the ring bearing R^6, and R^7 together form  . In some embodiments, L^1, L^2, and the ring bearing R^6, and R^7 together form  , or  .

[0186] In some embodiments of a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1, L^2, and the ring bearing R^6, and R^7 together form a heteroaryl selected from the group consisting of

 , and  . In some embodiments, L^1, L^2, and the

ring bearing R^6, and R^7 together form  , or  . In some embodiments, L^1, L^2, and the ring bearing R^6, and R^7 together  , or  .

[0187] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, *n* is 1 or 2, and L^2 is -O-. In some embodiments, *n* is 2, and L^2 is -O-. In some embodiments, *n* is 1, and L^2 is O. In some embodiments, *n* is 1 or 2, L^2 is -O- and R^4 is $-S(O)_2-R^a$. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0188] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, *n* is 1, *p* is 0, L^2 is O and each of X^1 and X^2 is $C(R^5)$, wherein each R^5 is independently H, halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH, and wherein the C_{1-6}alkoxy of R^5 is optionally substituted with one or more halo. In some embodiments, *n* is 1, *p* is 0, L^2 is O and each of X^1 and X^2 is $C(R^5)$, wherein each R^5 is independently H. In some embodiments, *n* is 1, *p* is 0, L^2 is O and each of X^1 and X^2 is $C(R^5)$, wherein one of R^5 is H and the other of R^5 is halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH, and wherein the C_{1-6}alkoxy is optionally substituted with one or more halo. In some embodiments, *n* is 1, *p* is 0, L^2 is O and each of X^1 and X^2 is $C(R^5)$, wherein each R^5 is independently halo, -CN, 3-10

membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH, and wherein the C_{1-6}alkoxy is optionally substituted with one or more halo. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0189] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, *n* is 1, *p* is 0, L^2 is O, one of X^1 and X^2 is N, and the other of X^1 and X^2 is $C(R^5)$, wherein R^5 is H, halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH, and wherein the C_{1-6}alkoxy of R^5 is optionally substituted with one or more halo. In some embodiments, *n* is 1, *p* is 0, L^2 is O, one of X^1 and X^2 is N, and the other of X^1 and X^2 is $C(R^5)$, wherein R^5 is H. In some embodiments, *n* is 1, *p* is 0, L^2 is O, one of X^1 and X^2 is N, and the other of X^1 and X^2 is $C(R^5)$, wherein R^5 is halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH, and wherein the C_{1-6}alkoxy of R^5 is optionally substituted with one or more halo. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0190] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, *n* is 1, L^2 is O, and each of X^1 and X^2 is N. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0191] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, *n* is 1, *p* is 0, L^2 is O, one of X^1 and X^2 is $C(R^5)$, wherein R^5 is H, the other of X^1 and X^2 is C that is taken together with R^4, and the atoms to which they are attached, to form (i) a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more of R^b, or (ii) a 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl is optionally substituted with one or more R^c, and each of R^6 and R^7 is H. In some variations, the embodiments provided herein also apply to a

compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0192] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, *n* is 1, L^2 is O, one of X^1 and X^2 is $C(R^5)$, wherein R^5 is H, halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH, and wherein the C_{1-6}alkoxy of R^5 is optionally substituted with one or more halo, the other of X^1 and X^2 is C that is taken together with R^4, and the atoms to which they are attached, to form (i) a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more of R^b, or (ii) a 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl is optionally substituted with one or more R^c, and each of R^6 and R^7 is H. In some embodiments, *n* is 1, L^2 is O, one of X^1 and X^2 is $C(R^5)$, wherein R^5 is H, the other of X^1 and X^2 is C that is taken together with R^4, and the atoms to which they are attached, to form (i) a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more of R^b, or (ii) a 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl is optionally substituted with one or more R^c, and each of R^6 and R^7 is H. In some embodiments, *n* is 1, L^2 is O, one of X^1 and X^2 is $C(R^5)$, wherein R^5 is halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH, and wherein the C_{1-6}alkoxy of R^5 is optionally substituted with one or more halo, the other of X^1 and X^2 is C that is taken together with R^4, and the atoms to which they are attached, to form (i) a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more of R^b, or (ii) a 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl is optionally substituted with one or more R^c, and each of R^6 and R^7 is H. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0193] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, *n* is 1, *p* is 0, L^2 is O, one of X^1 and X^2 is N, the other of X^1 and X^2 is C that is taken together with R^4, and the atoms to which they are attached, to form (i) a 5-10 membered heterocyclyl, wherein the 5-10 membered

heterocyclyl is optionally substituted with one or more of R^b, or (ii) a 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl is optionally substituted with one or more R^c, and each of R^6 and R^7 is H. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0194] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing:

m is an integer from 0 to 2;

n is an integer from 1 to 2;

p is an integer from 0 to 2;

R^1, if present is, independently at each occurrence selected from the group consisting of halo, -CN, C_{1-3}alkoxy, or C_{1-3}alkyl, wherein

the C_{1-3}alkoxy of R^1 is optionally substituted with one or more halo, and

the C_{1-3}alkyl of R^1 is optionally substituted with one or more halo;

R^2 is H, C_{1-3}alkyl, C_{3-6}cycloalkyl, or 3-10 membered heterocyclyl, wherein

the C_{1-3}alkyl of R^2 is optionally substituted with one or more halo, -OH, $-NH_2$, or C_{1-3}alkoxy, and

the C_{3-6}cycloalkyl of R^2 is optionally substituted with one or more -OH;

R^3, if present, is C_{1-3}alkyl;

L^1 is C_{1-3}alkylene, wherein the C_{1-3}alkylene of L^1 is optionally substituted with one or more C_{1-3}alkyl, and wherein the C_{1-3}alkyl is further optionally substituted with one or more -OH or C_{1-3}alkoxy;

L^2 is O or $N(R^x)$, wherein R^x is H or C_{1-3}alkyl; and

either

(1) L^3 is absent or is O, C_{3-6}cycloalkyl, 3-10 membered heterocyclyl, or C_{1-6}alkylene, wherein

the C_{3-6}cycloalkyl is optionally substituted with one or more -OH, or C_{1-3}alkyl,

the C_{1-3}alkylene of L^3 is optionally substituted with one or more -OH or C_{1-3}alkyl, and

the 3-10 membered heterocyclyl is optionally substituted with one or more -OH;

X^1 and X^2 are each independently N or $-C(R^5)$; and

R^4 is:

(i) $-S(O)_2-R^a$;

(ii) 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^4 is optionally substituted with one or more C_{1-3}alkyl;

(iii) $-N(R^d)_2$, wherein R^d is independently at each occurrence H, C_{1-3}alkyl, or $-S(O)_2-R^a$, wherein the C_{1-3}alkyl of R^d is optionally substituted with one or more -OH,

(iv) $-NS(O)-(C_{1-3}alkyl)_2$, wherein the C_{1-3}alkyl is optionally substituted with one or more –OH,

(v) $-C(O)-N(R^e)_2$ wherein R^e is independently at each occurrence H, C_{1-3}alkyl, or 3-10 membered heterocycle, wherein the 3-10 membered heterocycle is optionally substituted with one or more oxo, or both R^e together with the N to which they are attached are taken together to form a 3-10 membered heterocyclyl, wherein the 3-10 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, $-NH-S(O)_2-R^a$, or $-S(O)_2-R^a$,

(vi) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-3}alkyl, -OH , oxo or $-S(O)_2R^a$,

(vii) $-S(O)-N(C_{1-3}alkyl)-(C_{1-3}alkyl)$,

(viii) -CN,

(ix) $-(CH_2)_qOH$, wherein q is an integer from 0-4,

(x) $-C(O)-C_{1-3}$alkyl, or

(xi) $-P(O)(C_{1-3}alkyl)_2$;

or

(2) L^3 is absent; and

one of X^1 and X^2 is N or $C(R^5)$; and

the other of X^1 and X^2 is N or C that is taken together with R^4 and the atoms to which they are attached to form a 5-10 membered heterocyclyl or a 5-10 membered heteroaryl, wherein

the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is, independently at each occurrence, selected from the group consisting of halo, oxo, C_{1-3}alkyl, $-C(O)-C_{1-3}$alkyl, $-C(O)-NH_2$, $-C(O)-NH(C_{1-3}alkyl)$, $-C(O)-N(C_{1-3}alkyl)_2$, $-S(O)_2-R^a$, C_{3-6}cycloalkyl, and 3-6 membered heterocyclyl, wherein

the C_{1-3}alkyl of R^b is optionally substituted with one or more halo, OH, -$S(O)_2$-C_{1-3}alkyl, or C_{3-6}cycloalkyl, and

wherein the C_{3-6}cycloalkyl of the C_{1-3}alkyl of R^b is further optionally substituted with one or more C_{1-3}alkyl or -OH and

the C_{3-6}cycloalkyl of R^b is optionally substituted with one or more -OH, C_{3-6}cycloalkyl, or C_{1-3}alkyl, and

wherein the C_{1-3}alkyl of the C_{3-6}cycloalkyl of R^b is further optionally substituted with one or more -OH, and

the 5-10 membered heteroaryl is optionally substituted with one or more R^c, wherein R^c is, independently at each occurrence, selected from the group consisting of halo, C_{1-3}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-3}alkyl), -C(O)-N(C_{1-3}alkyl)$_2$, -$S(O)_2$-R^a, C_{3-6}cycloalkyl, and 3-6 membered heterocyclyl, wherein

the C_{1-3}alkyl of R^c is optionally substituted with one or more -$S(O)_2$-C_{1-6}alkyl,

the C_{3-6}cycloalkyl of R^c is optionally substituted with one or more -OH or C_{1-6}alkyl,

and the 3-6 membered heterocyclyl of R^c is optionally substituted with one or more -OH or C_{1-3}alkyl, and

wherein the C_{1-3}alkyl of the 3-6 membered heterocyclyl of R^c is further optionally substituted with one or more -OH;

R^a is, independently at each occurrence:

(i) C_{1-3}alkyl optionally substituted with one or more halo, -OH, -$S(O)_2$-C_{1-3}alkyl, or -N(C_{1-3}alkyl)-C(O)-C_{1-3}alkyl,

(ii) C_{3-6}cycloalkyl optionally substituted with one or more -OH, -$C(O)_2$-C_{1-3}alkyl, -C(O)-NH(C_{1-3}alkyl), -C(O)-N(C_{1-3}alkyl)$_2$, or –C(O)-C_{3-6}heterocyclyl, or C_{1-3}alkyl, wherein the C_{1-3}alkyl is optionally substituted with one or more -OH, or

(iii) 3-6 membered heterocyclyl optionally substituted with one or more C_{1-3}alkyl;

R^5 is, independently at each occurrence, H, halo, -CN, 3-6 membered heterocyclyl, C_{1-3}alkyl, or C_{1-3}alkoxy, wherein the C_{1-3}alkyl of R^5 is optionally substituted with one or more halo or -OH, and wherein the C_{1-3}alkoxy of R^5 is optionally substituted with one or more halo; and

R^6 and R^7 are each independently H or halo. In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0195] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing:

m is an integer from 0 to 2;

n is an integer from 1 to 2;

p is an integer from 0 to 1;

R^1, if present is, independently at each occurrence selected from the group consisting of Cl, Br, F, I, -CN, C_{1-3}alkoxy, or C_{1-3}alkyl, wherein

the C_{1-3}alkoxy of R^1 is optionally substituted with one or more F, and

the C_{1-3}alkyl of R^1 is optionally substituted with one or more F;

R^2 is H, C_{1-3}alkyl, C_{3-4}cycloalkyl, or 3-4 membered heterocyclyl, wherein

the C_{1-3}alkyl of R^2 is optionally substituted with one or more F, -OH, $-NH_2$, or $-OCH_3$, and

the C_{3-4}cycloalkyl of R^2 is optionally substituted with one or more -OH;

R^3, if present, is C_{1-3}alkyl;

L^1 is C_{1-3}alkylene, wherein the C_{13}alkylene of L^1 is optionally substituted with one or more methyl, and wherein the methyl is further optionally substituted with one or more -OH or $–OCH_3$;

L^2 is O; and

either

(1) L^3 is absent or is O, C_{3-4}cycloalkyl, 3-7 membered heterocyclyl, or C_{1-4}alkylene, wherein

the C_{3-4}cycloalkyl is optionally substituted with one or more -OH, or $-CH_3$,

the C_{1-6}alkylene of L^3 is optionally substituted with one or more -OH, $-CH_3$, and

X^1 and X^2 are each independently N or $C(R^5)$; and

R^4 is:

(i) $-S(O)_2-R^a$;

(ii) 5-6 membered heteroaryl, wherein the 5-6 membered heteroaryl of R^4 is optionally substituted with one or more $-CH_3$;

(iii) $-N(R^d)_2$, wherein R^d is independently at each occurrence H, C_{1-3}alkyl, or $-S(O)_2-R^a$, wherein the C_{1-3}alkyl of R^d is optionally substituted with one or more –OH,

(iv) -NS(O)-$(CH_3)_2$

(v) -C(O)-$N(R^e)_2$ wherein R^e is independently at each occurrence H, CH_3, or 3-6 membered heterocycle, wherein the 3-6 membered heterocycle is optionally substituted with one or more oxo, or both R^e together with the N to which they are attached are taken together to form a 3-7 membered heterocyclyl, wherein the 3-7 membered heterocyclyl is optionally substituted with one or more F, oxo, -OH, NH_2, -NH-$S(O)_2$-R^a, or -$S(O)_2$-R^a,

(vi) 3-7 membered heterocyclyl optionally substituted with one or more C_{1-3}alkyl, -OH , oxo or -$S(O)_2R^a$,

(vii) -S(O)-$N(CH_3)$-(CH_3),

(viii) -CN,

(ix) -$(CH_2)_q$OH, wherein *q* is an integer from 0-2, or

(x) -C(O)-CH_3, or

(xi) -$P(O)(CH_3)_2$;

or

(2) L^3 is absent; and

one of X^1 and X^2 is N or $C(R^5)$; and

the other of X^1 and X^2 is N or C that is taken together with R^4 and the atoms to which they are attached to form a 5-8 membered heterocyclyl or a 5-6 membered heteroaryl, wherein

the 5-8 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is, independently at each occurrence, selected from the group consisting of oxo, C_{1-3}alkyl, -C(O)-CH_3, -C(O)-NH_2, -C(O)-$NH(CH_3)$, -C(O)-$N(CH_3)_2$, -$S(O)_2$-R^a, C_{3-4}cycloalkyl, and 3-4 membered heterocyclyl, wherein

the C_{1-3}alkyl of R^b is optionally substituted with one or more F, OH, -$S(O)_2$-CH_3, or C_{3-4}cycloalkyl, and

wherein the C_{3-4}cycloalkyl of the C_{1-3}alkyl of R^b is further optionally substituted with one or more CH_3 or -OH and

the C_{3-4}cycloalkyl of R^b is optionally substituted with one or more -OH, C_{3-4}cycloalkyl, or C_{1-3}alkyl, and

wherein the C_{1-3}alkyl of the C_{3-4}cycloalkyl of R^b is further optionally substituted with one or more -OH, and

the 5-6 membered heteroaryl is optionally substituted with one or more R^c, wherein R^c is, independently at each occurrence, selected from the group consisting of C_{1-3}alkyl, -$S(O)_2$-R^a, C_{3-4}cycloalkyl, and 3-4 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more -$S(O)_2$-CH_3

the C_{3-4}cycloalkyl of R^c is optionally substituted with one or more –OH or C_{1-3}alkyl,

and the 3-4 membered heterocyclyl of R^c is optionally substituted with one or more -OH or methyl, and

wherein the methyl of the 3-4 membered heterocyclyl of R^c is further optionally substituted with one or more -OH;

R^a is, independently at each occurrence:

(i) C_{1-3}alkyl optionally substituted with one or more F, -OH, -$S(O)_2$-CH_3, or -$N(CH_3)$-C(O)-CH_3,

(ii) C_{3-4}cycloalkyl optionally substituted with one or more -OH, -$C(O)_2$-CH_3, -C(O)-$NH(CH_3)$, -C(O)-$N(CH_3)_2$, or -C(O)-C_{3-4}heterocyclyl, or methyl, wherein the methyl is optionally substituted with one or more -OH, or

(iii) 3-4 membered heterocyclyl optionally substituted with one or more methyl;

R^5 is, independently at each occurrence, H, Cl, F, -CN, 3-4 membered heterocyclyl, C_{1-3}alkyl, or C_{1-3}alkoxy, wherein the C_{1-3}alkyl of R^5 is optionally substituted with one or more F or -OH and wherein the C_{1-3}alkoxy of R^5 is optionally substituted with one or more F; and

R^6 and R^7 are each independently H or F. In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0196] In some embodiments of a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing,

m is an integer from 0 to 2;

n is an integer from 1 to 2;

p is an integer from 0 to 1;

R^1, if present is, independently at each occurrence selected from the group consisting of halo, -CN, C_{1-3}alkoxy, and C_{1-3}alkyl, wherein

the C_{1-3}alkoxy of R^1 is optionally substituted with one or more halo, and

the C_{1-3}alkyl of R^1 is optionally substituted with one or more halo;

R^2 is H, C_{1-3}alkyl, C_{3-6}cycloalkyl, or 3-6 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^2 is optionally substituted with one or more deuterium, halo, -OH, $-NH_2$, or C_{1-3}alkoxy, and

the C_{3-6}cycloalkyl of R^2 is optionally substituted with one or more -OH;

R^3, if present, is C_{1-3}alkyl;

L^1 is C_{1-3}alkylene, wherein

the C_{1-6}alkylene of L^1 is optionally substituted with one or more deuterium or C_{1-3}alkyl, and wherein

the C_{1-3}alkyl is further optionally substituted with one or more -OH or C_{1-3}alkoxy;

L^2 is O; and

either

(1) L^3 is absent or is O, C_{3-6}cycloalkyl, 3-6 membered heterocyclyl, or C_{1-3}alkylene, wherein

the C_{3-6}cycloalkyl of L^3 is optionally substituted with one or more -OH or C_{1-3}alkyl,

the C_{1-3}alkylene of L^3 is optionally substituted with one or more -OH or C_{1-3}alkyl, wherein

the C_{1-3}alkyl is optionally substituted with one or more -OH, and

the 3-6 membered heterocyclyl of L^3 is optionally substituted with one or more -OH or C_{1-3}alkyl;

X^1 and X^2 are each independently N or $C(R^5)$; and

R^4 is:

(i) $-S(O)_2-R^a$;

(ii) 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^4 is optionally substituted with one or more C_{1-3}alkyl;

(iii) $-N(R^d)_2$, wherein R^d is independently at each occurrence H, C_{1-3}alkyl, or $-S(O)_2-R^a$, wherein the C_{1-3}alkyl of R^d is optionally substituted with one or more -OH,

(iv) $-NS(O)-(C_{1-3}alkyl)_2$, wherein the C_{1-3}alkyl is optionally substituted with one or more –OH,

(v) $-C(O)-N(R^e)_2$ wherein R^e is independently at each occurrence H, C_{1-3}alkyl, or 3-6 membered heterocycle, wherein

the 3-6 membered heterocycle of R^e is optionally substituted with one or more oxo, or both R^e together with the N to which they are attached are taken together to form a 3-6 membered heterocyclyl, wherein

the 3-6 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, -NH-$S(O)_2$-R^a, or -$S(O)_2$-R^a,

(vi) 3-6 membered heterocyclyl optionally substituted with one or more C_{1-3}alkyl, -OH, oxo or -$S(O)_2R^a$,

(vii) -S(O)-N(C_{1-3}alkyl)-(C_{1-3}alkyl),

(viii) -CN,

(ix) -$(CH_2)_q$OH, wherein q is an integer from 0-3,

(x) -C(O)-C_{1-3}alkyl, or

(xi) -P(O)(C_{1-3}alkyl)$_2$;

or

(2) L^3 is absent; and

one of X^1 and X^2 is N or C(R^5); and

the other of X^1 and X^2 is N or C that is taken together with R^4, and the atoms to which they are attached, to form a 5-8 membered heterocyclyl or a 5-10 membered heteroaryl, wherein

the 5-8 membered heterocyclyl is optionally substituted with one or more R^b, wherein

R^b is, independently at each occurrence, selected from the group consisting of -OH, halo, oxo, C_{1-3}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-3}alkyl), -C(O)-N(C_{1-3}alkyl)$_2$, -$S(O)_2$-R^a, C_{3-6}cycloalkyl, and 3-6 membered heterocyclyl, wherein

the C_{1-3}alkyl of R^b is optionally substituted with one or more halo, OH, -$S(O)_2$-C_{1-3}alkyl, or C_{3-6}cycloalkyl, and wherein

the C_{3-6}cycloalkyl of the C_{1-3}alkyl of R^b is further optionally substituted with one or more C_{1-3}alkyl or -OH and

the C_{3-6}cycloalkyl of R^b is optionally substituted with one or more -OH, C_{3-6}cycloalkyl, or C_{1-3}alkyl, and wherein

the C_{1-3}alkyl of the C_{3-6}cycloalkyl of R^b is further optionally substituted with one or more -OH, deuterium, or halo, and

the 5-10 membered heteroaryl is optionally substituted with one or more R^c, wherein

R^c is, independently at each occurrence, selected from the group consisting of halo, C_{1-3}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-3}alkyl), -C(O)-N(C_{1-3}alkyl)$_2$, -$S(O)_2$-R^a, C_{3-6}cycloalkyl, and 3-6 membered heterocyclyl, wherein

the C_{1-3}alkyl of R^c is optionally substituted with one or more -$S(O)_2$-C_{1-3}alkyl,

the C_{3-6}cycloalkyl of R^c is optionally substituted with one or more -OH or C_{1-3}alkyl, and

the 3-6 membered heterocyclyl of R^c is optionally substituted with one or more -OH or C_{1-3}alkyl, and wherein

the C_{1-3}alkyl of the 3-6 membered heterocyclyl of R^c is further optionally substituted with one or more -OH;

R^a is, independently at each occurrence:

(i) C_{1-3}alkyl optionally substituted with one or more halo, -OH, -$S(O)_2$-C_{1-3}alkyl, or -N(C_{1-3}alkyl)-C(O)-C_{1-3}alkyl,

(ii) C_{3-6}cycloalkyl optionally substituted with one or more -OH, -$C(O)_2$-C_{1-3}alkyl, -C(O)-NH(C_{1-3}alkyl), -C(O)-N(C_{1-3}alkyl)$_2$, or -C(O)-C_{3-6}heterocyclyl, or C_{1-3}alkyl, wherein

the C_{1-3}alkyl is optionally substituted with one or more -OH,

(iii) 3-6 membered heterocyclyl optionally substituted with one or more C_{1-3}alkyl, or

(iv) NH(C_{1-3}alkyl);

R^5 is, independently at each occurrence, H, halo, -CN, 3-6 membered heterocyclyl, C_{1-3}alkyl, or C_{1-3}alkoxy, wherein

the C_{1-3}alkyl of R^5 is optionally substituted with one or more halo or -OH, and

the C_{1-3}alkoxy of R^5 is optionally substituted with one or more halo;

X^3 is N or C(R^6);

X^4 is N or C(R^7);

and

R^6 and R^7 are each independently H or halo.

[0197] In some embodiments of a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing,

m is an integer from 0 to 2;

n is 1;

p is an integer from 0;

R^1, if present is, independently at each occurrence selected from the group consisting of halo, -CN, C_{1-3}alkoxy, and C_{1-3}alkyl, wherein

the C_{1-3}alkoxy of R^1 is optionally substituted with one or more halo, and

the C_{1-3}alkyl of R^1 is optionally substituted with one or more halo;

R^2 is H, C_{1-3}alkyl, C_{3-6}cycloalkyl, or 3-6 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^2 is optionally substituted with one or more deuterium, halo, -OH, $-NH_2$, or C_{1-3}alkoxy, and

the C_{3-6}cycloalkyl of R^2 is optionally substituted with one or more -OH;

L^1 is C_{1-3}alkylene, wherein

the C_{1-6}alkylene of L^1 is optionally substituted with one or more deuterium;

L^2 is O; and

either

(1) L^3 is absent or is O, C_{3-6}cycloalkyl, 3-6 membered heterocyclyl, or C_{1-3}alkylene, wherein

the C_{3-6}cycloalkyl of L^3 is optionally substituted with one or more -OH or C_{1-3}alkyl,

the C_{1-3}alkylene of L^3 is optionally substituted with one or more -OH or C_{1-3}alkyl, wherein

the C_{1-3}alkyl is optionally substituted with one or more -OH, and

the 3-6 membered heterocyclyl of L^3 is optionally substituted with one or more -OH or C_{1-3}alkyl;

X^1 and X^2 are each independently N or $C(R^5)$; and

R^4 is:

(i) $-S(O)_2-R^a$;

(ii) 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^4 is optionally substituted with one or more C_{1-3}alkyl;

(iii) $-N(R^d)_2$, wherein R^d is independently at each occurrence H, C_{1-3}alkyl, or $-S(O)_2-R^a$, wherein the C_{1-3}alkyl of R^d is optionally substituted with one or more -OH,

(iv) $-NS(O)-(C_{1-3}alkyl)_2$, wherein the C_{1-3}alkyl is optionally substituted with one or more –OH,

(v) $-C(O)-N(R^e)_2$ wherein R^e is independently at each occurrence H, C_{1-3}alkyl, or 3-6 membered heterocycle, wherein

the 3-6 membered heterocycle of R^e is optionally substituted with one or more oxo, or both R^e together with the N to which they are attached are taken together to form a 3-6 membered heterocyclyl, wherein

the 3-6 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, -NH-$S(O)_2$-R^a, or -$S(O)_2$-R^a,

(vi) 3-6 membered heterocyclyl optionally substituted with one or more C_{1-3}alkyl, -OH, oxo or -$S(O)_2R^a$,

(ix) -$(CH_2)_q$OH, wherein q is an integer from 0-3;

or

(2) L^3 is absent; and

one of X^1 and X^2 is N or C(R^5); and

the other of X^1 and X^2 is N or C that is taken together with R^4, and the atoms to which they are attached, to form a 5-8 membered heterocyclyl or a 5-10 membered heteroaryl, wherein

the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein

R^b is, independently at each occurrence, selected from the group consisting of -OH, halo, oxo, C_{1-3}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-3}alkyl), -C(O)-N(C_{1-3}alkyl)$_2$, -$S(O)_2$-R^a, C_{3-6}cycloalkyl, and 3-6 membered heterocyclyl, wherein

the C_{1-3}alkyl of R^b is optionally substituted with one or more halo, OH, -$S(O)_2$-C_{1-3}alkyl, or C_{3-6}cycloalkyl, and wherein

the C_{3-6}cycloalkyl of the C_{1-3}alkyl of R^b is further optionally substituted with one or more C_{1-3}alkyl or -OH and

the C_{3-6}cycloalkyl of R^b is optionally substituted with one or more -OH, C_{3-6}cycloalkyl, or C_{1-3}alkyl, and wherein

the C_{1-3}alkyl of the C_{3-6}cycloalkyl of R^b is further optionally substituted with one or more -OH, deuterium, or halo, and

the 5-10 membered heteroaryl is optionally substituted with one or more R^c, wherein

R^c is, independently at each occurrence, selected from the group consisting of halo, C_{1-3}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-3}alkyl), -C(O)-N(C_{1-3}alkyl)$_2$, -$S(O)_2$-R^a, C_{3-6}cycloalkyl, and 3-6 membered heterocyclyl, wherein

the C_{1-3}alkyl of R^c is optionally substituted with one or more -$S(O)_2$-C_{1-3}alkyl,

the C_{3-6}cycloalkyl of R^c is optionally substituted with one or more -OH or C_{1-3}alkyl, and

the 3-6 membered heterocyclyl of R^c is optionally substituted with one or more -OH or C_{1-3}alkyl, and wherein

the C_{1-3}alkyl of the 3-6 membered heterocyclyl of R^c is further optionally substituted with one or more -OH;

R^a is, independently at each occurrence:

(i) C_{1-3}alkyl optionally substituted with one or more halo, -OH, -$S(O)_2$-C_{1-3}alkyl, or -$N(C_{1-3}$alkyl)-C(O)-C_{1-3}alkyl,

(ii) C_{3-6}cycloalkyl optionally substituted with one or more -OH, -$C(O)_2$-C_{1-3}alkyl, -C(O)-$NH(C_{1-3}$alkyl), -C(O)-$N(C_{1-3}alkyl)_2$, or -C(O)-C_{3-6}heterocyclyl, or C_{1-3}alkyl, wherein

the C_{1-3}alkyl is optionally substituted with one or more -OH,

(iii) 3-6 membered heterocyclyl optionally substituted with one or more C_{1-3}alkyl, or

(iv) $NH(C_{1-3}$alkyl);

R^5 is, independently at each occurrence, H, halo, -CN, 3-6 membered heterocyclyl, C_{1-3}alkyl, or C_{1-3}alkoxy, wherein

the C_{1-3}alkyl of R^5 is optionally substituted with one or more halo or -OH, and

the C_{1-3}alkoxy of R^5 is optionally substituted with one or more halo;

X^3 is N or $C(R^6)$;

X^4 is N or $C(R^7)$;

and

R^6 and R^7 are each independently H or halo.

[0198] In some embodiments of a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing,

m is an integer from 0 to 2;

n is 1;

p is an integer from 0;

R^1, if present is, independently at each occurrence selected from the group consisting of halo, -CN, C_{1-3}alkoxy, and C_{1-3}alkyl, wherein

the C_{1-3}alkoxy of R^1 is optionally substituted with one or more halo, and

the C_{1-3}alkyl of R^1 is optionally substituted with one or more halo;

R^2 is H;

L^1 is C_{1-3}alkylene, wherein

the C_{1-6}alkylene of L^1 is optionally substituted with one or more deuterium;

L^2 is O; and

either

(1) L^3 is absent or is C_{1-3}alkylene, wherein

the C_{1-3}alkylene of L^3 is optionally substituted with one or more -OH or C_{1-3}alkyl;

X^1 and X^2 are each independently N or $C(R^5)$; and

R^4 is:

(i) $-S(O)_2-R^a$;

(ii) $-(CH_2)_qOH$, wherein q is an integer from 0-3;

or

(2) L^3 is absent; and

one of X^1 and X^2 is N or $C(R^5)$; and

the other of X^1 and X^2 is N or C that is taken together with R^4, and the atoms to which they are attached, to form a 5-8 membered heterocyclyl or a 5-20 membered heteroaryl, wherein

the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein

R^b is, independently at each occurrence oxo, or C_{3-6}cycloalkyl, wherein the C_{3-6}cycloalkyl is optionally substituted with one or more -OH, C_{3-6}cycloalkyl, or C_{1-3}alkyl, and

the 5-10 membered heteroaryl is optionally substituted with one or more R^c, wherein

R^c is, independently at each occurrence, selected from the group consisting of C_{1-3}alkyl, C_{3-6}cycloalkyl, wherein the C_{3-6}cycloalkyl of R^c is optionally substituted with one or more -OH or C_{1-3}alkyl;

R^a is, independently at each occurrence:

(i) C_{1-3}alkyl optionally substituted with one or more halo, -OH, $-S(O)_2-C_{1-3}$alkyl, or $-N(C_{1-3}$alkyl$)-C(O)-C_{1-3}$alkyl;

R^5 is, independently at each occurrence, H, halo, C_{1-3}alkyl, or C_{1-3}alkoxy, wherein

the C_{1-3}alkyl of R^5 is optionally substituted with one or more halo or -OH, and

the C_{1-3}alkoxy of R^5 is optionally substituted with one or more halo;

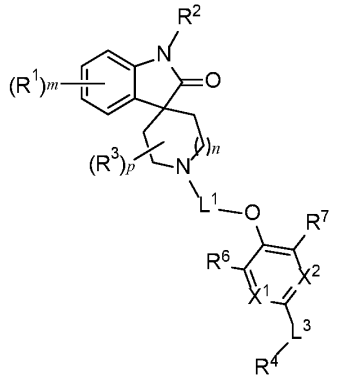
X^3 is N or $C(R^6)$;

X^4 is N or $C(R^7)$;

and

R^6 and R^7 are each independently H or halo.

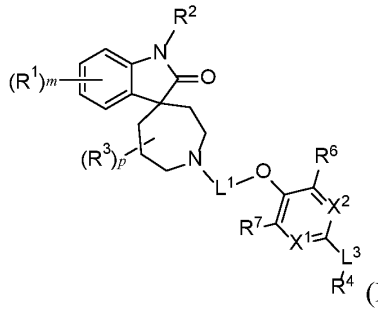
[0199] In some embodiments, provided herein is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is a compound of formula (I-A):



(I-A),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein: *n* is 1 or 2; and *m*, *p*, R^1, R^2, R^3, L^1, L^3, R^4, X^1, X^2, R^6, and R^7 are as defined for formula (I). In some variations *m*, *p*, R^1, R^2, R^3, L^1, L^3, R^4, X^1, X^2, R^6, and R^7 of formula (I-A) are as defined for a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0200] In some embodiments, provided herein is a compound of formula (I) or formula (I-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is a compound of formula (I-A1):



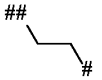
(I-A1),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein: *m*, *p*, R^1, R^2, R^3, L^1, L^3, R^4, X^1, X^2, R^6, and R^7 are as defined for formula (I). In some variations *m*, *p*, R^1, R^2, R^3, L^1, L^3, R^4, X^1, X^2, R^6, and R^7 of formula (I-A1) are as defined for a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0201] In some embodiments of a compound of formula (I), (I-A) or (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is H. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0202] In some embodiments of a compound of formula (I), (I-A) or (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, *m* is an integer from 0 to 4. In some embodiments, *m* is an integer from 0 to 2. In some embodiments, *m* is 0. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0203] In some embodiments of a compound of formula (I), (I-A) or (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, *p* is an integer from 0 to 10. In some embodiments, *p* is 0 or 1. In some embodiments, *p* is 0. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0204] In some embodiments of a compound of formula (I), (I-A) or (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1 is C_{1-6}alkylene. In some embodiments, L^1 is C_{1-3}alkylene. In some embodiments, L^1 is ethylene. In some embodiments, L^1 is  wherein, # denotes the point of attachment to -O- and ## denotes the point of attachment to the remainder of the molecule. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0205] In some embodiments of a compound of formula (I), (I-A) or (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is absent. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0206] In some embodiments of a compound of formula (I), (I-A) or (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is $-S(O)_2-R^a$, wherein R^a is C_{1-6}alkyl. In some embodiments, R^4 is $-S(O)_2-R^a$, wherein R^a is C_{1-3}alkyl. In some embodiments, R^4 is $-S(O)_2-R^a$, wherein R^a is methyl. In some embodiments, R^4 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

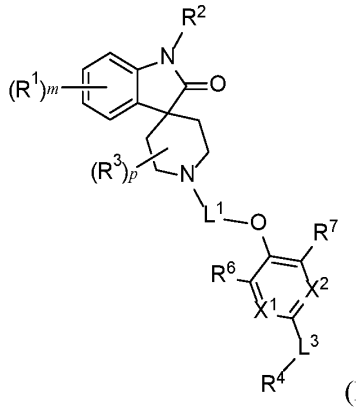
[0207] In some embodiments of a compound of formula (I), (I-A) or (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, each of X^1 and X^2 is $C(R^5)$. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0208] In some embodiments of a compound of formula (I), (I-A) or (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^5 is H. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a

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

[0209] In some embodiments of a compound of formula (I), (I-A) or (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, each of R^6 and R^7 is H. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

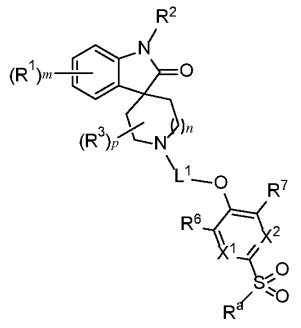
[0210] In some embodiments, provided herein is a compound of formula (I) or formula (I-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is a compound of formula (I-A2):



(I-A2),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein m, p, R^1, R^2, R^3, L^1, L^3, R^4, X^1, X^2, R^6, and R^7 are as defined for formula (I). In some variations, m, p, R^1, R^2, R^3, L^1, L^3, R^4, X^1, X^2, R^6, and R^7 of formula (I-A2) are as defined for a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

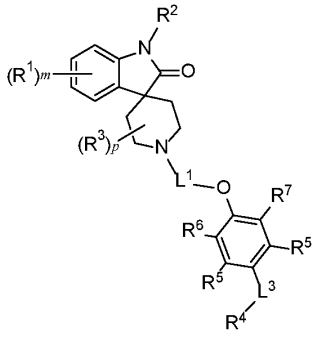
[0211] In some embodiments, provided herein is a compound of formula (I) or formula (I-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is a compound of formula (I-A3):



(I-A3),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein: n is 1 or 2; and wherein m, n, p, R^1, R^2, R^3, L^1, X^1, X^2, R^6, R^7, and R^a are as defined for formula (I). In some variations, m, n, p, R^1, R^2, R^3, L^1, X^1, X^2, R^6, R^7, and R^a of formula (I-A3) are as defined for a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

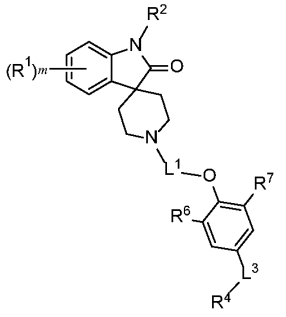
[0212] In some embodiments, provided herein is a compound of formula (I), (I-A), or (I-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-B):



(I-B),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein: m, p, R^1, R^2, R^3, L^1, L^3, R^4, R^5, R^6, and R^7 are as defined for formula (I). In some variations, m, p, R^1, R^2, R^3, L^1, L^3, R^4, R^5, R^6, and R^7 of formula (I-B) are as defined for a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0213] In some embodiments, provided herein is a compound of formula (I), (I-A), (I-A2), or (I-B), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-B1):



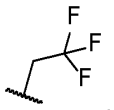
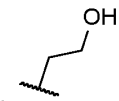
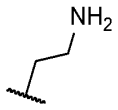
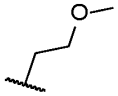
(I-B1),

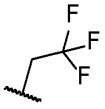
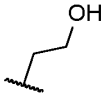
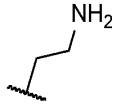
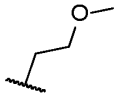
or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein: *m*, R^1, R^2, L^1, L^3, R^4, R^6, and R^7 are as defined for formula (I). In some variations, *m*, R^1, R^2, L^1, L^3, R^4, R^6, and R^7 of formula (I-B1) are as defined for a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

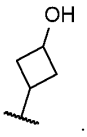
[0214] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is H. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0215] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl. In some embodiments, R^2 is C_{1-3}alkyl. In some embodiments, R^2 is methyl. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

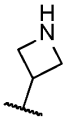
[0216] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl optionally substituted with one or more halo, -OH, or C_{1-6}alkoxy. In some embodiments, R^2 is C_{1-3}alkyl optionally substituted with one or more halo, -OH, or C_{1-3}alkoxy. In some

embodiments, R^2 is ethyl optionally substituted with one or more halo, -OH, NH_2, or C_{1-3}alkoxy. In some embodiments, R^2 is selected from the group consisting of  ,  ,  and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0217] In some embodiments of a compound of formula (II), such as a compound of formula (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl optionally substituted with one or more deuterium, halo, -OH, or C_{1-6}alkoxy. In some embodiments, R^2 is C_{1-3}alkyl optionally substituted with one or more deuterium, halo, -OH, or C_{1-3}alkoxy. In some embodiments, R^2 is methyl optionally substituted with one or more deuterium halo, -OH, NH_2, or C_{1-3}alkoxy. In some embodiments, R^2 is ethyl optionally substituted with one or more deuterium halo, -OH, NH_2, or C_{1-3}alkoxy. In some embodiments, R^2 is selected from the group consisting of  ,  ,  ,  and  .

[0218] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{3-10}cycloalkyl optionally substituted with one or more -OH. In some embodiments, R^2 is C_{3-6} cycloalkyl optionally substituted with one or more -OH. In some embodiments, R^2 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0219] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is 3-15 membered heterocyclyl. In some embodiments, R^2 is 3-6 membered heterocyclyl. In some

embodiments, R^2 is  , or  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0220] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, *m* is an integer from 0 to 4. In some embodiments, *m* is an integer from 0 to 2. In some embodiments, *m* is 0. In some embodiments *m* is 1. In some embodiments, *m* is 2. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0221] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is halo. In some embodiments R^1 is Cl. In some embodiments, R^1 is Br. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

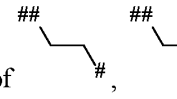
[0222] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is $C_{1\text{-}6}$alkyl. In some embodiments, R^1 is methyl. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0223] In some embodiments of a compound of formula (I'), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is $C_{1\text{-}6}$alkyl, wherein the $C_{1\text{-}6}$alkyl of R^1 is optionally substituted with one or more halo. In some embodiments, R^1 is $C_{1\text{-}3}$alkyl, wherein the $C_{1\text{-}3}$alkyl of R^1 is optionally substituted with one or more halo. In some embodiments, R^1 is methyl, wherein the methyl of R^1 is optionally substituted with

one or more F. In some embodiemtns. R^1 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0224] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is -CN. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

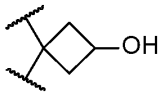
[0225] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, *p* is an integer from 0 to 10. In some embodiments, *p* is 0. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0226] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1 is $C_{1\text{-}6}$alkylene, wherein the $C_{1\text{-}6}$alkylene of L^1 is optionally substituted with one or more $C_{1\text{-}6}$alkyl. In some embodiments, L^1 is $C_{1\text{-}3}$alkylene optionally substituted with one or more $C_{1\text{-}3}$alkyl. In some embodiments, L^1 is ethylene optionally substituted with one or more $C_{1\text{-}6}$alkyl. In some embodiments, L^1 is selected from the group consisting of  , wherein, for each L^1, # denotes the point of attachment to -O- and ## denotes the point of attachment to the remainder of the molecule. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

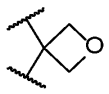
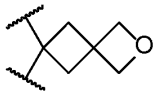
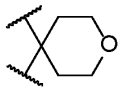
[0227] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is absent. In some variations, the embodiments provided herein also apply to a compound of formula

(I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

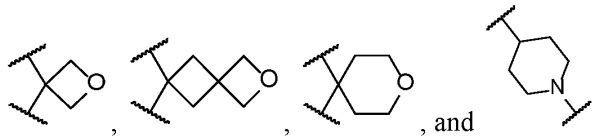
[0228] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is C_{1-6}alkylene. In some embodiments, L^3 C_{1-3}alkylene. In some embodiments, L^3 is selected from the group consisting of  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0229] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of L^3 is optionally substituted with one or more -OH. In some embodiments, L^3 is C_{3-8}cycloalkyl, wherein the C_{3-8}cycloalkyl of L^3 is optionally substituted with one or more -OH. In some embodiments, L^3 is selected from the group consisting of  ,  , and 

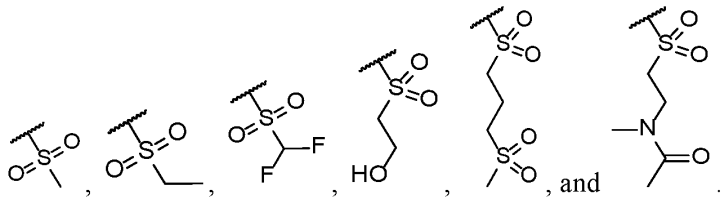
. In some variations, the embodiments provided herein also apply to a compound of formula (I') or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0230] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is 3-10 membered heterocyclyl. In some embodiments, L^3 is 3-6 membered heterocyclyl. In some embodiments, L^3 is selected from the group consisting of  ,  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0231] In some embodiments of a compound of formula (II), such as a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is 3-10 membered heterocyclyl. In some embodiments, L^3 is 3-6 membered heterocyclyl. In some embodiments, L^3 is selected from the group consisting of

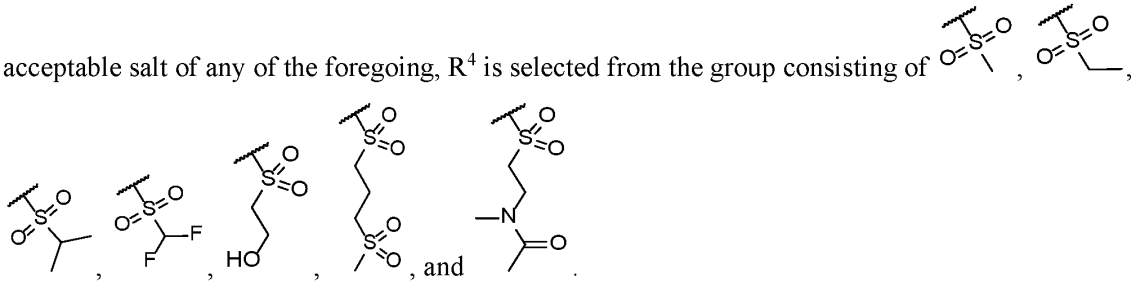


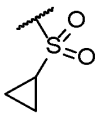
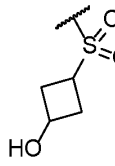
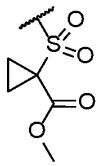
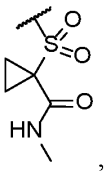
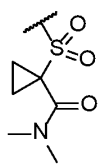
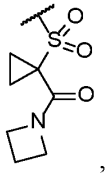
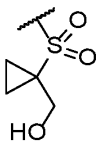
[0232] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is $-S(O)_2-R^a$, wherein R^a is C_{1-6}alkyl. In some embodiments, R^4 is $-S(O)_2-R^a$, wherein R^a is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^a is optionally substituted with one or more halo, -OH, $-S(O)_2-C_{1-6}$alkyl, or $-N(C_{1-6}$alkyl$)-C(O)-C_{1-6}$alkyl. In some embodiments, R^4 is $-S(O)_2-R^a$, wherein R^a is C_{1-3}alkyl, wherein the C_{1-3}alkyl of R^a is optionally substituted with one or more halo, -OH, $-S(O)_2-C_{1-3}$alkyl, or $-N(C_{1-3}$alkyl$)-C(O)-C_{1-3}$alkyl. In some embodiments, R^4 is selected from the group consisting of



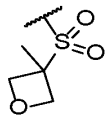
. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

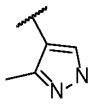
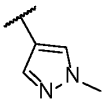
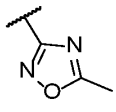
[0233] In some embodiments of a compound of formula (II), such as a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is selected from the group consisting of

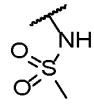
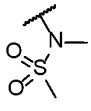


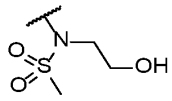
[0234] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is $-S(O)_2-R^a$, wherein R^a is C_{3-10}cycloalkyl. R^4 is $-S(O)_2-R^a$, wherein R^a is C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of R^a is optionally substituted with one or more -OH, $C(O)_2-C_{1-6}$alkyl, $-C(O)-NH(C_{1-6}alkyl)$, $-C(O)-N(C_{1-6}alkyl)_2$, $-C(O)-C_{3-10}$heterocyclyl or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more -OH. In some embodiments, R^4 is $-S(O)_2-R^a$, wherein R^a is C_{3-6}cycloalkyl, wherein the C_{3-6}cycloalkyl of R^a is optionally substituted with one or more -OH, $C(O)_2-C_{1-6}$alkyl, $-C(O)-NH(C_{1-6}alkyl)$, $-C(O)-N(C_{1-6}alkyl)_2$, $-C(O)-C_{3-10}$heterocyclyl, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more -OH. In some embodiments, R^4 is $-S(O)_2-R^a$, wherein R^a is C_{3-6}cycloalkyl, wherein the C_{3-6}cycloalkyl of R^a is optionally substituted with one or more -OH, $C(O)_2-C_{1-3}$alkyl, $-C(O)-NH(C_{1-3}alkyl)$, $-C(O)-N(C_{1-3}alkyl)_2$, $-C(O)-C_{3-6}$heterocyclyl, or C_{1-3}alkyl, wherein the C_{1-3}alkyl is optionally substituted with one or more -OH. In some embodiments, R^4 is selected from the group consisting of  ,  ,  ,  ,  ,  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0235] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is $-S(O)_2-R^a$, wherein R^a is 3-10 membered heterocyclyl. In some embodiments R^4 is $-S(O)_2-R^a$, wherein R^a is 3-10 membered heterocyclyl, wherein the 3-10 membered heterocyclyl of R^a is optionally substituted with one or more C_{1-6}alkyl. In some embodiments, R^4 is $-S(O)_2-R^a$, wherein R^a is 3-6 membered heterocyclyl, wherein the 3-6 membered heterocyclyl of R^a is optionally substituted with one or more C_{1-6}alkyl. In some embodiments, wherein R^4 is $-S(O)_2-R^a$, wherein R^a is 3-6 membered heterocyclyl, wherein the 3-6 membered heterocyclyl of R^a is optionally

substituted with one or more C_{1-3}alkyl. In some embodiments, R^4 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

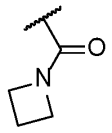
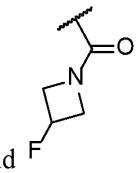
[0236] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1) or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is 5-20 membered heteroaryl. In some embodiments, R^4 is 5-20 membered heteroaryl optionally substituted with one or more C_{1-6}alkyl. In some embodiments, R^4 is 5-6 membered heteroaryl optionally substituted with one or more C_{1-6}alkyl. In some embodiments, R^4 is 5-6 membered heteroaryl optionally substituted with one or more C_{1-3}alkyl. In some embodiments, R^4 is 5-6 membered heteroaryl optionally substituted with one or more methyl. In some embodiments, R^4 is selected from the group consisting of  ,  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

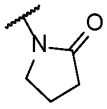
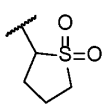
[0237] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is $-N(R^d)_2$, wherein each of R^d is independently H, or C_{1-6} alkyl, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more –OH or $-S(O)_2-R^a$, wherein R^a is C_{1-6}alkyl. In some embodiments, R^4 is $-N(R^d)_2$, wherein each of R^d is independently H, or C_{1-3} alkyl, wherein the C_{1-3}alkyl of R^d is optionally substituted with one or more –OH, or $-S(O)_2-R^a$, wherein R^a is C_{1-3}alkyl. In some embodiments, R^4 is $-N(R^d)_2$, wherein each of R^d is independently H, or C_{1-3}alkyl, wherein the C_{1-3}alkyl of R^d is optionally substituted with one or more –OH or $-S(O)_2-R^a$, wherein R^a is methyl. In some embodiments, R^4 is selected from the group consisting of $-NH_2$,  ,  , and

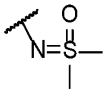
 . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0238] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is -C(O)-N(R^e)$_2$, wherein each of R^e is independently H or C_{1-6} alkyl. In some embodiments, R^4 is -C(O)-N(R^e)$_2$, wherein each of R^e is independently H or C_{1-3} alkyl. In some embodiments, R^4 is -C(O)-N(R^e)$_2$, wherein each of R^e is independently H or methyl. In some embodiments, R^4 is -C(O)-NH_2. In some embodiments, R^4 is -C(O)-NH(CH_3). In some embodiments, R^4 is -C(O)-N(CH_3)$_2$. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0239] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is -C(O)-N(R^e)$_2$, wherein both R^e together with the N to which they are attached are taken together to form a 3-10 membered heterocyclyl. In some embodiments R^4 is –C(O)-N(R^e)$_2$, wherein both R^e together with the N to which they are attached are taken together to form a 3-10 membered heterocyclyl, wherein the 3-10 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, NH-S(O)$_2$-R^a, or -S(O)$_2$-R^a, wherein R^a is C_{1-6}alkyl. In some embodiments R^4 is –C(O)-N(R^e)$_2$, wherein both R^e together with the N to which they are attached are taken together to form a 3-7 membered heterocyclyl, wherein the 3-7 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, NH-S(O)$_2$-R^a, or -S(O)$_2$-R^a, wherein R^a is C_{1-3}alkyl. In some embodiments R^4 is –C(O)-N(R^e)$_2$, wherein both R^e together with the N to which they are attached are taken together to form a 3-7 membered heterocyclyl, wherein the 3-7 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, NH-S(O)$_2$-R^a, or -S(O)$_2$-R^a, wherein R^a is methyl. In some embodiments, R^4 is selected from the group consisting of


, and 
. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0240] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is 3-10 membered heterocyclyl optionally substituted with one or more oxo. In some embodiments, R^4 is 3-7 membered heterocyclyl optionally substituted with one or more oxo. In some embodiments, R^4 is selected from the group consisting of 
, and 
. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0241] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is -NS(O)-(C_{1-6}alkyl)$_2$. In some embodiments, R^4 is -NS(O)-(C_{1-3}alkyl)$_2$. In some embodiments, wherein R^4 is 
. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

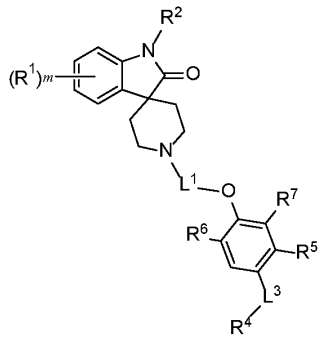
[0242] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is -S(O)-N(C_{1-6}alkyl)-(C_{1-6}alkyl). In some embodiments, R^4 is -S(O)-N(C_{1-3}alkyl)-(C_{1-3}alkyl). In some embodiments, R^4 is 
. In some variations, the embodiments provided herein also apply to a

compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0243] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is -CN. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0244] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is -P(O)(C_{1-6}alkyl)$_2$. In some embodiments, R^4 is -P(O)(C_{1-3}alkyl)$_2$. In some embodiments, R^4 is -P(O)(CH_3)$_2$. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0245] In some embodiments, provided herein is a compound of formula (I), (I-A), (I-A2), or (I-B), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-B2):

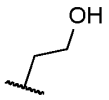


(I-B2),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein: R^5 is halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH and wherein the C_{1-6}alkoxy is optionally substituted with one or more halo; and *m*, R^1, R^2, L^1, L^3, R^4, R^6, and R^7 are as defined for formula (I). In some variations, *m*, R^1, R^2, L^1, L^3, R^4, R^6, and R^7 of formula (I-B2) are as

defined for a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0246] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is H. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0247] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more halo, -OH. In some embodiments, R^2 is C_{1-3}alkyl, wherein the C_{1-3}alkyl of R^2 is optionally substituted with one or more halo, -OH. In some embodiments, R^2 is methyl. In some embodiments, R^2 is ethyl, wherein the ethyl of R^2 is optionally substituted with one or more halo, -OH. In some embodiments, R^2 is 

. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0248] In some embodiments of a compound of formula (II), such as a compounf of formula (I), (I-A), (I-A2), (I-B), or (I-B2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more deuterium. In some embodiments, R^2 is C_{1-3}alkyl, wherein the C_{1-3}alkyl of R^2 is optionally substituted with one or more deuterium. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is optionally substituted with one of more deuterium. In some embodiments, R^2 is 

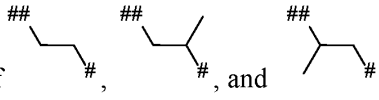
.

[0249] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, *m* is 1. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or

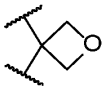
(II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0250] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is halo. In some embodiments R^1 is Cl. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

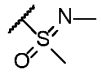
[0251] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is -CN. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0252] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1 is C_{1-6}alkylene optionally substituted with one or more C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with -OH or C_{1-6}alkoxy. In some embodiments, L^1 is methylene. In some embodiments, L^1 is ethylene optionally substituted with one or more C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more -OH or C_{1-6}alkoxy. In some embodiments, L^1 is selected from the group consisting of  , wherein, for each L^1, # denotes the point of attachment to -O- and ## denotes the point of attachment to the remainder of the molecule. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0253] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is absent. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0254] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is 3-10 membered heterocyclyl. In some embodiments, L^3 is 3-6 membered heterocyclyl. In some embodiments, L^3 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

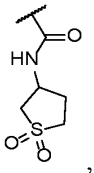
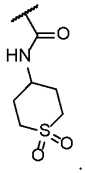
[0255] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is $-S(O)_2-R^a$, wherein R^a is C_{1-6}alkyl. In some embodiments, R^4 is $-S(O)_2-R^a$, wherein R^a is C_{1-6}alkyl. In some embodiments, R^4 is $-S(O)_2-R^a$, wherein R^a is C_{1-3}alkyl. In some embodiments, R^4 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0256] In some embodiments of a compound of formula (II) such as a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is $-NS(O)-(C_{1-6}alkyl)_2$. In some embodiments, R^4 is $-NS(O)-(C_{1-6}alkyl)_2$. In some embodiments, R^4 is $-NS(O)-(C_{1-3}alkyl)_2$. In some embodiments, R^4 is  .

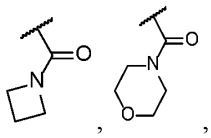
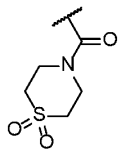
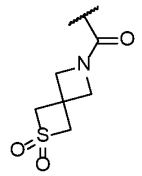
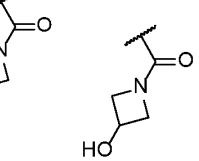
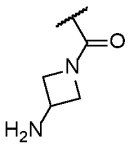
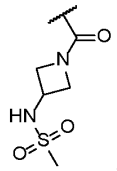
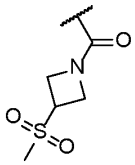
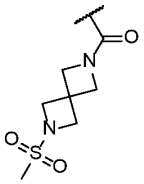
[0257] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is $-N(R^d)_2$, wherein each of R^d is independently H, C_{1-6} alkyl, or $-S(O)_2-R^a$, wherein R^a is C_{1-6}alkyl. In some embodiments, R^4 is $-N(R^d)_2$, wherein each of R^d is independently H, C_{1-3} alkyl, or $-S(O)_2-R^a$, wherein R^a is C_{1-3}alkyl. In some embodiments, R^4 is $-N(R^d)_2$, wherein each of R^d is independently H, C_{1-6} alkyl, or $-S(O)_2-R^a$, wherein R^a is methyl. In some embodiments, R^4 is selected from the group consisting of $-NH_2$, and  . In some variations, the embodiments provided herein also

apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0258] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is -C(O)-N(R^e)$_2$, wherein each of R^e is independently H or C_{1-6} alkyl. In some embodiments, R^4 is -C(O)-N(R^e)$_2$, wherein each of R^e is independently H or C_{1-3} alkyl. In some embodiments, R^4 is -C(O)-N(R^e)$_2$, wherein each of R^e is independently H or methyl. In some embodiments, R^4 is -C(O)-NH_2. In some embodiments, R^4 is -C(O)-NH(CH_3). In some embodiments, R^4 is -C(O)-N(CH_3)$_2$. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0259] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is –C(O)-N(R^e)$_2$, wherein each of R^e is independently H or 3-10 membered heterocycle, wherein the 3-10 membered heterocycle is optionally substituted with one or more oxo. In some embodiments, R^4 is –C(O)-N(R^e)$_2$, wherein each of R^e is independently H or 3-6 membered heterocycle, wherein the 3-6 membered heterocycle is optionally substituted with one or more oxo. In some embodiments, R^4 is selected from the group consisting of  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

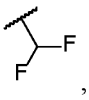
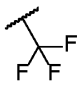
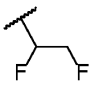
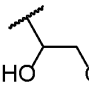
[0260] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is -C(O)-N(R^e)$_2$, wherein both R^e together with the N to which they are attached are taken together to form a 3-10 membered heterocyclyl. In some embodiments R^4 is -C(O)-N(R^e)$_2$, wherein both R^e together with the N to which they are attached are taken together to form a 3-10 membered heterocyclyl, wherein the 3-10 membered heterocyclyl is optionally substituted with one or more

oxo, -OH, NH_2, or $-S(O)_2-R^a$, wherein R^a is C_{1-6}alkyl. In some embodiments R^4 is $-C(O)-N(R^e)_2$, wherein both R^e together with the N to which they are attached are taken together to form a 3-7 membered heterocyclyl, wherein the 3-7 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, $NH-S(O)_2-R^a$, or $-S(O)_2-R^a$, wherein R^a is C_{1-3}alkyl. In some embodiments R^4 is $-C(O)-N(R^e)_2$, wherein both R^e together with the N to which they are attached are taken together to form a 3-7 membered heterocyclyl, wherein the 3-7 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, $NH-S(O)_2-R^a$, or $-S(O)_2-R^a$, wherein R^a is methyl. In some embodiments, R^4 is selected from the group consisting of  , ,  ,  ,  ,  ,  ,  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

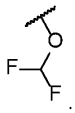
[0261] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^5 is halo. In some embodiments, R^5 is Cl, or F. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0262] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^5 is -CN. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0263] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^5 is

C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH. In some embodiments, R^5 is C_{1-3}alkyl, wherein the C_{1-3}alkyl of R^5 is optionally substituted with one or more halo, or -OH. In some embodiments, R^5 is C_{1-3}alkyl, wherein the C_{1-3}alkyl of R^5 is optionally substituted with one or more fluoro, or -OH. In some embodiments, R^5 is selected from the group consisting of methyl,  ,  ,  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

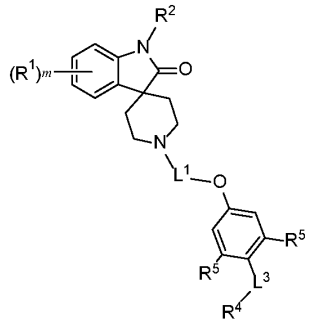
[0264] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^5 is 3-10 membered heterocyclyl. In some embodiments, R^5 is 3-6 membered heterocyclyl. In some embodiments, R^5 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0265] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^5 is C_{1-6}alkoxy, wherein the C_{1-6}alkoxy is optionally substituted with one or more halo. In some embodiments R^5 is C_{1-3}alkoxy, wherein the C_{1-3}alkoxy is optionally substituted with one or more halo. In some embodiments, R^5 is C_{1-3}alkoxy, wherein the C_{1-3}alkoxy is optionally substituted with one or more fluoro. In some embodiments, R^5 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0266] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^6

and R^7 are each independently H or halo. In some embodiments, R^6 and R^7 are each independently H or fluoro. In some embodiments, each of R^6 and R^7 is H. In some embodiments, one of R^6 and R^7 is H and the other of R^6 and R^7 is fluoro. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0267] In some embodiments, provided herein is a compound of formula (I), (I-A), (I-A2), or (I-B), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-B3):



(I-B3),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein: each R^5 is, independently at each occurrence, halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH and wherein the C_{1-6}alkoxy is optionally substituted with one or more halo; and m, R^1, R^2, L^1, L^3, R^4, R^6, and R^7 are as defined for formula (I). In some variations, m, R^1, R^2, L^1, L^3, R^4, R^6, and R^7 of formula (I-B3) are as defined for a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

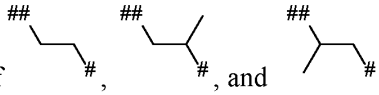
[0268] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is H. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0269] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is $C_{1\text{-}6}$alkyl. In some embodiments, R^2 is methyl. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0270] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, *m* is an integer from 0 to 4. In some embodiments, *m* is 0 or 1. In some embodiments, *m* is 0. In some embodiments *m* is 1. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0271] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is halo. In some embodiments R^1 is Cl. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0272] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is -CN. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0273] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1 is $C_{1\text{-}6}$alkylene optionally substituted with one or more $C_{1\text{-}6}$alkyl, wherein the $C_{1\text{-}6}$alkyl is optionally substituted with -OH or $C_{1\text{-}6}$alkoxy. In some embodiments, L^1 is methylene. In some embodiments, L^1 is ethylene optionally substituted with one or more $C_{1\text{-}6}$alkyl, wherein the $C_{1\text{-}6}$alkyl is optionally substituted with one or more -OH or $C_{1\text{-}6}$alkoxy. In some embodiments, L^1 is selected from the group consisting of  , wherein, for each L^1, # denotes the point of

attachment to -O- and ## denotes the point of attachment to the remainder of the molecule. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0274] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is absent. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

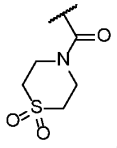
[0275] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is C_{1-6}alkylene. In some embodiments, L^3 is C_{1-3}alkylene. In some embodiments, L^3 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0276] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is 3-10 membered heterocyclyl. In some embodiments, L^3 is 3-6 membered heterocyclyl. In some embodiments, L^3 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0277] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is $-S(O)_2-R^a$, wherein R^a is C_{1-6}alkyl. In some embodiments, R^4 is $-S(O)_2-R^a$, wherein R^a is C_{1-6}alkyl. In some embodiments, R^4 is $-S(O)_2-R^a$, wherein R^a is C_{1-3}alkyl. In some embodiments, R^4 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or

(II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

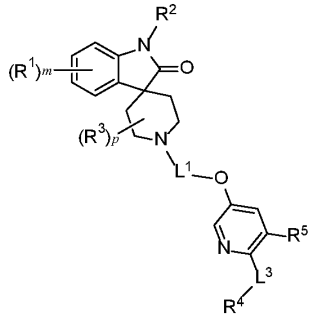
[0278] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is $-N(R^d)_2$, wherein each of R^d is independently C_{1-6} alkyl, or $-S(O)_2-R^a$, and wherein R^a is C_{1-6}alkyl. In some embodiments, R^4 is $-N(R^d)_2$, wherein each of R^d is independently C_{1-3} alkyl, or $-S(O)_2-R^a$, wherein R^a is C_{1-3}alkyl. In some embodiments, R^4 is $-N(R^d)_2$, wherein each of R^d is methyl, or $-S(O)_2-R^a$, wherein R^a is methyl. In some embodiments, R^4 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0279] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is $-C(O)-N(R^e)_2$, wherein both R^e together with the N to which they are attached are taken together to form a 3-10 membered heterocyclyl, wherein the 3-10 membered heterocyclyl is optionally substituted with one or more oxo. In some embodiments R^4 is $-C(O)-N(R^e)_2$, wherein both R^e together with the N to which they are attached are taken together to form a 3-7 membered heterocyclyl, wherein the 3-7 membered heterocyclyl is optionally substituted with one or more oxo. In some embodiments, R^4 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0280] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-B), or (I-B3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^5 is, independently at each occurrence selected from the group consisting of, halo and C_{1-6}alkyl. In some embodiments, R^5 is, independently at each occurrence selected from the group consisting of halo and C_{1-3}alkyl. In some embodiments, R^5 is, independently at each occurrence, selected from the

group consisting of F and methyl. In some embodiments, each R^5 is F. In some embodiments, each R^5 is methyl. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

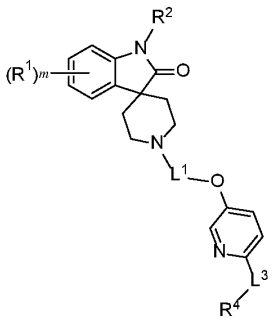
[0281] In some embodiments, provided herein is a compound of formula (I), (I-A), or (I-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-C):



(I-C),

[0282] or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein: *m*, *p*, R^1, R^2, R^3, L^1, L^3, R^4, and R^5 are as defined for formula (I). In some variations *m*, *p*, R^1, R^2, R^3, L^1, L^3, R^4, and R^5 of formula (I-C) are as defined for a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0283] In some embodiments, provided herein is a compound of formula (I), (I-A), (I-A2), or (I-C), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-C1):



(I-C1),

[0284] or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein: *m*, R^1, R^2, R^3, L^1, L^3, and R^4, are as defined for formula (I). In some variations *m*, R^1, R^2, R^3, L^1, L^3, and R^4 of formula (I-C) are as defined for a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

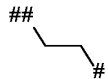
[0285] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-C), or (I-C1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is H. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0286] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-C), or (I-C1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, *m* is an integer from 0 to 4. In some embodiments, *m* is an integer from 0 to 2. In some embodiments *m* is 1. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0287] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-C), or (I-C1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is halo. In some embodiments R^1 is Cl. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0288] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-C), or (I-C1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is -CN. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0289] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-C), or (I-C1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1 is

C_{1-6}alkylene. In some embodiments, L^1 is ethylene. In some embodiments, L^1 is 

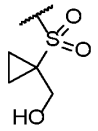
wherein, # denotes the point of attachment to -O- and ## denotes the point of attachment to the remainder of the molecule. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

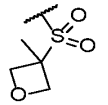
[0290] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-C), or (I-C1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is absent. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0291] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-C), or (I-C1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is C_{1-6}alkylene. In some embodiments, L^3 is C_{1-3}alkylene. In some embodiments, L^3 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0292] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-C), or (I-C1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is $-S(O)_2-R^a$, wherein R^a is C_{1-6}alkyl. In some embodiments, R^4 is $-S(O)_2-R^a$, wherein R^a is C_{1-3}alkyl. In some embodiments, R^4 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0293] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-C), or (I-C1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is $-S(O)_2-R^a$, wherein R^a is C_{3-10}cycloalkyl. R^4 is $-S(O)_2-R^a$, wherein R^a is C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of R^a is optionally substituted with one or more C_{1-6}alkyl, and wherein the C_{1-6}alkyl

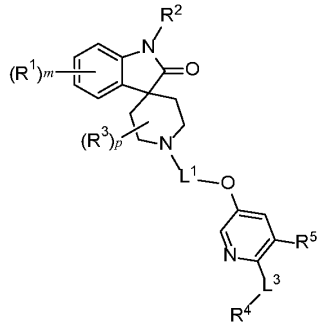
is optionally substituted with one or more -OH. In some embodiments, R^4 is $-S(O)_2-R^a$, wherein R^a is C_{3-6}cycloalkyl, wherein the C_{3-6}cycloalkyl of R^a is optionally substituted with one or more C_{1-6}alkyl, and wherein the C_{1-6}alkyl is optionally substituted with one or more -OH. In some embodiments, R^4 is $-S(O)_2-R^a$, wherein R^a is C_{3-6}cycloalkyl, wherein the C_{3-6}cycloalkyl of R^a is optionally substituted with one or more C_{1-3}alkyl, wherein the C_{1-3}alkyl is optionally substituted with one or more -OH. In some embodiments, R^4 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0294] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-C), or (I-C1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is $-S(O)_2-R^a$, wherein R^a is 3-10 membered heterocyclyl. In some embodiments R^4 is $-S(O)_2-R^a$, wherein R^a is 3-10 membered heterocyclyl, wherein the 3-10 membered heterocyclyl of R^a is optionally substituted with one or more C_{1-6}alkyl. In some embodiments, R^4 is $-S(O)_2-R^a$, wherein R^a is 3-6 membered heterocyclyl, wherein the 3-6 membered heterocyclyl of R^a is optionally substituted with one or more C_{1-6}alkyl. In some embodiments, wherein R^4 is $-S(O)_2-R^a$, wherein R^a is 3-6 membered heterocyclyl, wherein the 3-6 membered heterocyclyl of R^a is optionally substituted with one or more C_{1-3}alkyl. In some embodiments, R^4 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0295] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-C), or (I-C1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is $-C(O)-N(R^e)_2$, wherein each of R^e is independently H or C_{1-6} alkyl. In some embodiments, R^4 is $-C(O)-N(R^e)_2$, wherein each of R^e is independently H or C_{1-3} alkyl. In some embodiments, R^4 is $-C(O)-N(R^e)_2$, wherein each of R^e is independently H or methyl. In some embodiments, R^4 is -C(O)-

NH_2. In some embodiments, R^4 is -C(O)-N(CH_3)$_2$. In some embodiments, R^4 is -C(O)-NH_2. In some embodiments, R^4 is -C(O)-NH(CH_3). In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0296] In some embodiments, provided herein is a compound of formula (I), (I-A), or (I-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-C2):



(I-C2),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein: R^5 is, halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH and wherein the C_{1-6}alkoxy is optionally substituted with one or more halo; *m*, *p*, R^1, R^2, R^3, L^1, L^3, and R^4, are as defined for formula (I). In some variations, R^5 is halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH and wherein the C_{1-6}alkoxy of R^5 is optionally substituted with one or more halo; *m*, *p*, R^1, R^2, R^3, L^1, L^3, and R^4 of formula (I-C2) are as defined for a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

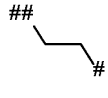
[0297] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-C), or (I-C2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is H. In some variations, the embodiments provided herein also apply to a compound of formula (I'). or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0298] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-C), or (I-C2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, *m* is an integer from 0 to 4. In some embodiments, *m* is an integer from 0 to 2. In some embodiments *m* is 1. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0299] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-C), or (I-C2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is halo. In some embodiments R^1 is Cl. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0300] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-C), or (I-C2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is -CN. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

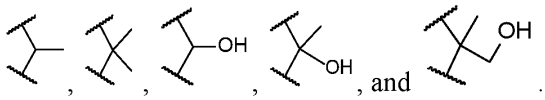
[0301] In some embodiments of a compound of formula (I'), (I-A), (I-A2), (I-C), or (I-C2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is $C_{1\text{-}6}$alkyl, wherein the $C_{1\text{-}6}$alkyl of R^1 is optionally substituted with one or more halo. In some embodiments, R^1 is $C_{1\text{-}3}$alkyl, wherein the $C_{1\text{-}3}$alkyl of R^1 is optionally substituted with one or more halo. In some embodiments, R^1 is methyl, wherein the methyl of R^1 is optionally substituted with one or more F. In some embodiemtns. R^1 is  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0302] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-C), or (I-C2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1 is $C_{1\text{-}6}$alkylene. In some embodiments, L^1 is ethylene. In some embodiments, L^1 is  , wherein,

denotes the point of attachment to -O- and ## denotes the point of attachment to the remainder of the molecule. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

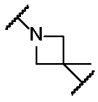
[0303] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-C), or (I-C2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is absent. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0304] In some embodiments of a compound formula (I'), (I-A), (I-A2), (I-C), or (I-C2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is C_{1-6}alkylene, wherein the C_{1-6}alkylene of L^3 is optionally substituted with one or more -OH, or C_{1-6}alkyl. In some embodiments, L^3 is C_{1-3}alkylene, wherein the C_{1-6}alkylene of L^3 is optionally substituted with one or more -OH, or C_{1-6}alkyl. In some embodiments, L^3 is selected from the group consisting of  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

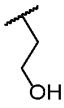
[0305] In some embodiments of a compound formula (II), such as a compound of formula (I'), (I-A), (I-A2), (I-C), or (I-C2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is C_{1-6}alkylene, wherein the C_{1-6}alkylene of L^3 is optionally substituted with one or more -OH, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more -OH. In some embodiments, L^3 is C_{1-3}alkylene, wherein the C_{1-6}alkylene of L^3 is optionally substituted with one or more -OH, or C_{1-3}alkyl, wherein the C_{1-3}alkyl is optionally substituted with one or more -OH. In some embodiments, L^3 is selected from the group consisting of  .

[0306] In some embodiments of a compound of formula (I'), (I), (I-A), (I-A2), (I-B), or (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing,

L^3 is C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of L^3 is optionally substituted with one or more -OH. In some embodiments, L^3 is C_{3-8}cycloalkyl, wherein the C_{3-8}cycloalkyl of L^3 is optionally substituted with one or more -OH. In some embodiments, L^3 is  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0307] In some embodiments of a compound formula (II), such as a compound of formula (I'), (I-A), (I-A2), (I-C), or (I-C2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is 3-10 membered heterocyclyl, optionally substituted with one or more -OH or C_{1-6}alkyl. In some embodiments, L^3 is 3-6 membered heterocyclyl, optionally substituted with one or more -OH or C_{1-3}alkyl. In some embodiments, L^3 is  .

[0308] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-C), or (I-C2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is $-S(O)_2-R^a$, wherein R^a is C_{1-6}alkyl. In some embodiments, R^4 is $-S(O)_2-R^a$, wherein R^a is C_{1-3}alkyl. In some embodiments, R^4 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0309] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-C), or (I-C2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is $-(CH_2)_qOH$, wherein q is an integer from 0-6. R^4 is $-(CH_2)_qOH$, wherein q is an integer from 0-2. In some embodiments, R^4 is -OH. In some embodiments, R^4 is selected from the group consisting of  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

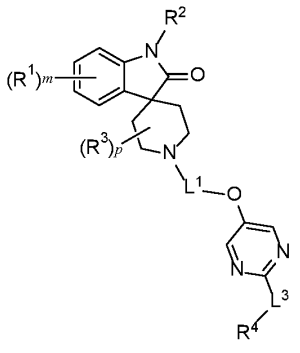
[0310] In some embodiments of a compound of formula (I'), (I-A), (I-A2), (I-C), or (I-C2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is -C(O)-C_{1-6}alkyl. In some embodiments, R^4 is -C(O)-C_{1-3}alkyl. In some embodiments, R^4 is -C(O)CH_3. In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0311] In some embodiments of a compound of formula (I), (I-A), (I-A2), (I-C), or (I-C2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^5 is C_{1-6}alkyl. In some embodiments, R^5 is C_{1-3}alkyl. In some embodiments, R^5 is methyl. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0312] In some embodiments of a compound of formula (I'), (I-A), (I-A2), (I-C), or (I-C2) or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^5 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo. In some embodiments, R^5 is C_{1-3}alkyl, wherein the C_{1-3}alkyl of R^5 is optionally substituted with one or more halo. In some embodiments, R^5 is C_{1-3}alkyl, wherein the C_{1-3}alkyl of R^5 is optionally substituted with one or more fluoro. In some embodiments, R^5 is  . In some embodiments, R^5 is methyl. In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0313] In some embodiments of a compound of formula (I'), (I-A), (I-A2), (I-C), or (I-C2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^5 is halo. In some embodiments, R^5 is Cl, or F. In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0314] In some embodiments, provided herein is a compound of formula (I), (I-A), or (I-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-D):



(I-D),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein: *m*, *p*, R^1, R^2, R^3, L^1, L^3, and R^4, are as defined for formula (I). In some variations, *m*, *p*, R^1, R^2, R^3, L^1, L^3, and R^4 of formula (I-D) are as defined for a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0315] In some embodiments of a compound of formula (I), (I-A), (I-A2), or (I-D), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is H. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0316] In some embodiments of a compound of formula (II), such as a compound of formula (I), (I-A), (I-A2), or (I-D), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is $C_{1\text{-}6}$alkyl optionally substituted with one or more deuterium. In some embodiments, R^2 is $C_{1\text{-}3}$alkyl optionally substituted with one or more deuterium. In some embodiments, R^2 is methyl optionally substituted with one or more deuterium. In some embodiments, R^2 is  .

[0317] In some embodiments of a compound of formula (I), (I-A), (I-A2), or (I-D), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, *m* is an integer from 0 to 4. In some embodiments, *m* is an integer from 0 to 2. In some embodiments *m* is 1. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or

(II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0318] In some embodiments of a compound of formula (I), (I-A), (I-A2), or (I-D), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is halo. In some embodiments R^1 is Cl. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0319] In some embodiments of a compound of formula (II), such as a compound of formula (I), (I-A), (I-A2), or (I-D), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is Cl, or I.

[0320] In some embodiments of a compound of formula (I), (I-A), (I-A2), or (I-D), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is -CN. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0321] In some embodiments of a compound of formula (I), (I-A), (I-A2), or (I-D), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is $C_{1\text{-}6}$alkyl, wherein the $C_{1\text{-}6}$alkyl of R^1 is optionally substituted with one or more halo. In some embodiments, R^1 is $C_{1\text{-}3}$alkyl, wherein the $C_{1\text{-}3}$alkyl of R^1 is optionally substituted with one or more halo. In some embodiments, R^1 is $C_{1\text{-}3}$alkyl, wherein the $C_{1\text{-}3}$alkyl of R^1 is optionally substituted with one or more F. In some embodiments, R^1 is methyl, wherein the methyl of R^1 is optionally substituted with one or more F. In some embodiments, R^1 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0322] In some embodiments of a compound of formula (I), (I-A), (I-A2), or (I-D), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1 is $C_{1\text{-}6}$alkylene optionally substituted with one or more $C_{1\text{-}6}$alkyl. In some embodiments, L^1 is ethylene optionally substituted with one or more $C_{1\text{-}6}$alkyl. In some embodiments, L^1 is selected from the

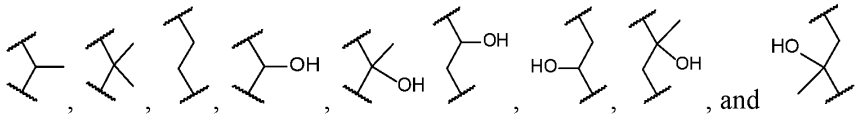
group consisting of  wherein, for each L^1, # denotes the point of attachment to -O- and ## denotes the point of attachment to the remainder of the molecule. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0323] In some embodiments of a compound of formula (I), (I-A), (I-A2), or (I-D), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is absent. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

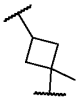
[0324] In some embodiments of a compound of formula (I), (I-A), (I-A2), or (I-D), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is -O-. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

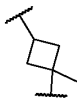
[0325] In some embodiments of a compound of formula (I), (I-A), (I-A2), or (I-D), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is C_{1-6}alkylene. In some embodiments, L^3 is C_{1-3}alkylene. In some embodiments, L^3 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0326] In some embodiments of a compound of formula (I'), (I-A), (I-A2), or (I-D), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is C_{1-6}alkylene, wherein the C_{1-6}alkylene of L^3 is optionally substituted with one or more -OH, or C_{1-6}alkyl. In some embodiments, L^3 is C_{1-3}alkylene, wherein the C_{1-6}alkylene of L^3 is optionally

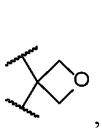
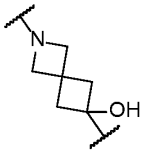
substituted with one or more -OH, or C_{1-6}alkyl. In some embodiments, L^3 is selected from the group consisting of  , and .

[0327] In some embodiments of a compound of formula (I), (I-A), (I-A2), or (I-D), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is C_{3-10}cycloalkyl. In some embodiments, L^3 is C_{3-8}cycloalkyl. In some embodiments, L^3 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0328] In some embodiments of a compound of formula (I'), (I-A), (I-A2), or (I-D), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of L^3 is optionally substituted with one or more -OH. In some embodiments, L^3 is C_{3-8}cycloalkyl, wherein the C_{3-8}cycloalkyl of L^3 is optionally substituted with one or more -OH. In some embodiments, L^3 is selected from the group consisting of  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0329] In some embodiments of a compound of formula (II), such as a compound of formula (I'), (I-A), (I-A2), or (I-D), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of L^3 is optionally substituted with one or more -OH. In some embodiments, L^3 is C_{3-8}cycloalkyl, wherein the C_{3-8}-cycloalkyl of L^3 is optionally substituted with one or more -OH. In some embodiments, L^3 is selected from the group consisting of  ,  , and  .

[0330] In some embodiments of a compound of formula (I'), (I-A), (I-A2), or (I-D) or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is 3-10 membered heterocyclyl. In some embodiments, L^3 is 3-6 membered heterocyclyl. In some embodiments, L^3 is selected from the group consisting of  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

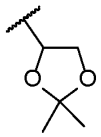
[0331] In some embodiments of a compound of formula (II), such as a compound of (I'), (I-A), (I-A2), or (I-D) or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^3 is 3-10 membered heterocyclyl. In some embodiments, L^3 is 3-6 membered heterocyclyl. In some embodiments, L^3 is selected from the group consisting of  ,  ,  and .

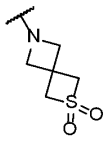
[0332] In some embodiments of a compound of formula (I), (I-A), (I-A2), or (I-D), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is $-S(O)_2-R^a$, wherein R^a is C_{1-6}alkyl. In some embodiments, R^4 is $-S(O)_2-R^a$, wherein R^a is C_{1-3}alkyl. In some embodiments, R^4 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0333] In some embodiments of a compound of formula (I), (I-A), (I-A2), or (I-D), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is $-C(O)-N(R^e)_2$, wherein each of R^e is H. In some embodiments, R^4 is $-C(O)-NH_2$. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer

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

[0334] In some embodiments of a compound of formula (I), (I-A), (I-A2), or (I-D), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6} alkyl. In some embodiments, R^4 is 3-6 membered heterocyclyl optionally substituted with one or more C_{1-6} alkyl. In some embodiments, R^4 is 3-6 membered heterocyclyl optionally substituted with one or more C_{1-3} alkyl. In some embodiments, R^4 is 3-6 membered heterocyclyl optionally substituted with one or more methyl. In some embodiments, R^4 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0335] In some embodiments of a compound of formula (II), such as a compound of formula (I), (I-A), (I-A2), or (I-D), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is  , or  .

[0336] In some embodiments of a compound of formula (I'), (I-A), (I-A2), or (I-D), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6} alkyl. In some embodiments, R^4 is 3-6 membered heterocyclyl optionally substituted with one or more C_{1-6} alkyl. In some embodiments, R^4 is 3-6 membered heterocyclyl optionally substituted with one or more C_{1-3} alkyl. In some embodiments, R^4 is 3-6 membered heterocyclyl optionally substituted with one or more methyl. In some embodiments, R^4 is selected from the group consisting of  , and  . In some variations, the embodiments provided herein also apply to a compound of formula

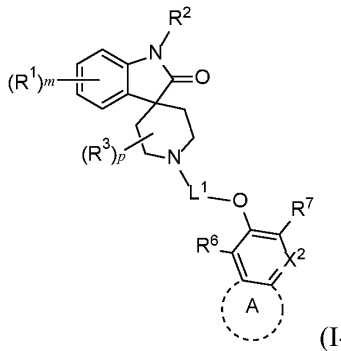
(II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0337] In some embodiments of a compound of formula (I'), (I-A), (I-A2), or (I-D) or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is $-(CH_2)_qOH$, wherein q is an integer from 0-6. R^4 is $-(CH_2)_qOH$, wherein q is an integer from 0-2. In some embodiments, R^4 is -OH. In some embodiments, R^4 is selected from the group consisting of  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0338] In some embodiments of a compound of formula (I'), (I-A), (I-A2), or (I-D) or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is $-N(R^d)_2$, wherein each of R^d is independently H. In some embodiments, R^4 is $-NH_2$. In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0339] In some embodiments of a compound of formula (I'), (I-A), (I-A2), or (I-D) or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is $-P(O)(C_{1\text{-}6}alkyl)_2$. In some embodiments, R^4 is $-P(O)(C_{1\text{-}3}alkyl)_2$. In some embodiments, R^4 is $-P(O)(CH_3)_2$. In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

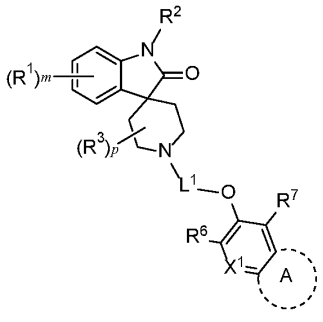
[0340] In some embodiments, provided herein is a compound of formula (I), (I-A) or (I-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-E):



(I-E),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein: ring A is 5-10 membered heterocyclyl or a 5-10 membered heteroaryl, wherein the 5-10 membered heterocyclyl of ring A is optionally substituted with one or more R^b, and wherein the 5-10 membered heteroaryl of ring A is optionally substituted with one or more R^c; and m, p, R^1, R^2, R^3 L^1, X^2, R^b, R^c, R^6, and R^7 are as defined for formula (I). In some variations, ring A is 5-10 membered heterocyclyl or a 5-10 membered heteroaryl, wherein the 5-10 membered heterocyclyl of ring A is optionally substituted with one or more R^b, and wherein the 5-10 membered heteroaryl of ring A is optionally substituted with one or more R^c; and m, p, R^1, R^2, R^3 L^1, X^2, R^b, R^c, R^6, and R^7 of formula (I-E) are as defined for a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

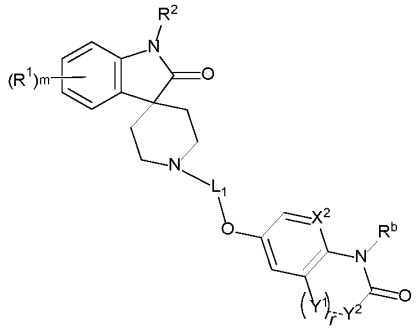
[0341] In some embodiments, provided herein is a compound of formula (I), (I-A) or (I-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-E1):



(I-E1),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein: ring A is 5-10 membered heterocyclyl or a 5-10 membered heteroaryl, wherein the 5-10 membered heterocyclyl of ring A is optionally substituted with one or more R^b, and wherein the 5-10 membered heteroaryl of ring A is optionally substituted with one or more R^c; and m, p, R^1, R^2, R^3, L^1, X^1, R^b, R^c, R^6, and R^7 are as defined for formula (I). In some variations, ring A is 5-10 membered heterocyclyl or a 5-10 membered heteroaryl, wherein the 5-10 membered heterocyclyl of ring A is optionally substituted with one or more R^b, and wherein the 5-10 membered heteroaryl of ring A is optionally substituted with one or more R^c; and m, p, R^1, R^2, R^3, L^1, X^1, R^b, R^c, R^6, and R^7 of formula (I-E1) are as defined for a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

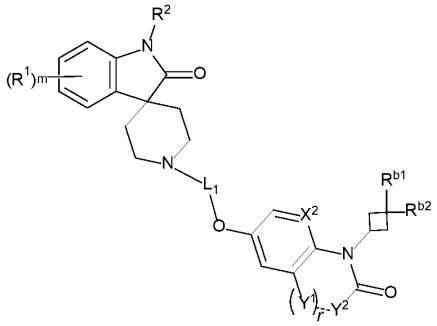
[0342] In some embodiments, provided herein is a compound of formula (I'), (I-A), (I-A2), or (I-E) or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-E2):



(I-E2),

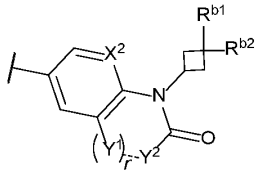
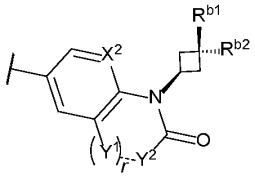
or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein: r is an integer from 0-1; Y^1 and Y^2 are each independently C or N, optionally substituted by one or more H or R^b; and m, R^1, R^2, L^1, X^2, and R^b are as defined for formula (I'), or (II); and wherein the dashed line represents a single or double bond.

[0343] In some embodiments, provided herein is a compound of formula (I'), (I-A), (I-A2), or (I-E) or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-E3):

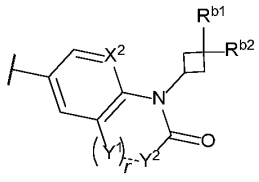
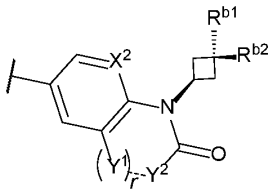


(I-E3),

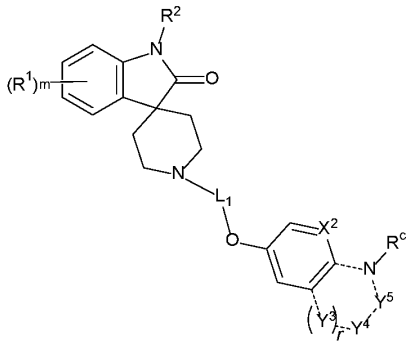
or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein: *r* is an integer from 0-1; Y^1 and Y^2 are each independently C or N, optionally substituted by one or more H or R^b; R^{b1} is OH; R^{b2} is H, C_{1-6}alkyl, or C_{3-10}cycloalkyl, wherein the C_{1-6}alkyl of R^{b2} is optionally substituted with one or more OH; and *m*, R^1, R^2, L^1, X^2, and R^b are as defined for formula (I'), or (II); and wherein the dashed line represents a single or double bond.

[0344] In some embodiments of a compound of formula (I'), (I-A) (I-A2), or (I-E3) or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, the moiety represented by  , has a stereochemical configuration represented by  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0345] In some embodiments of a compound of formula (I'), (I-A) (I-A2), or (I-E3) or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, the

moiety represented by  , has a stereochemical configuration represented by  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

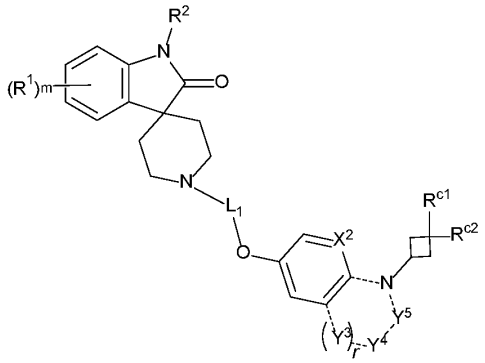
[0346] In some embodiments, provided herein is a compound of formula (I'), (I-A), (I-A2), or (I-E) or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-E4):



[0347] (I-E4),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein: r is an integer from 0-1; Y^2, Y^3 and Y^4 are each independently C or N, optionally substituted by one or more H or R^c; and m, R^1, R^2, L^1, X^2, and R^c are as defined for formula (I'), or (II); and wherein the dashed line represents a single or double bond.

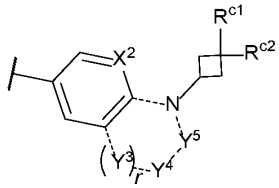
[0348] In some embodiments, provided herein is a compound of formula (I'), (I-A), (I-A2), or (I-E) or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-E5):



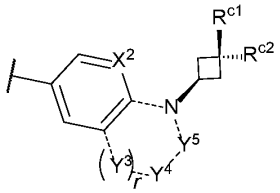
(I-E5),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein: *r* is an integer from 0-1; Y^3, Y^4 and Y^5 are each independently C or N, optionally substituted by one or more H or R^c; R^{c1} is OH; R^{c2} is H, $C_{1\text{-}6}$alkyl, or $C_{3\text{-}10}$cycloalkyl, wherein the $C_{1\text{-}6}$alkyl of R^{c2} is optionally substituted with one or more OH; and *m*, R^1, R^2, L^1, X^2, and R^c are as defined for formula (I'), or (II); and wherein the dashed line represents a single or double bond.

[0349] In some embodiments of a compound of formula (I'), (I-A) (I-A2), or (I-E5) or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, the

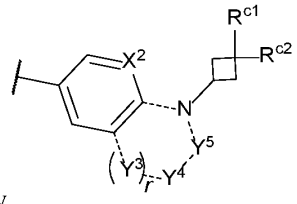


moiety represented by , has a stereochemical configuration represented by

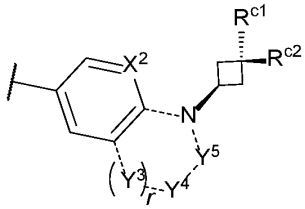


. In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0350] In some embodiments of a compound of formula (I'), (I-A) (I-A2), or (I-E) or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, the

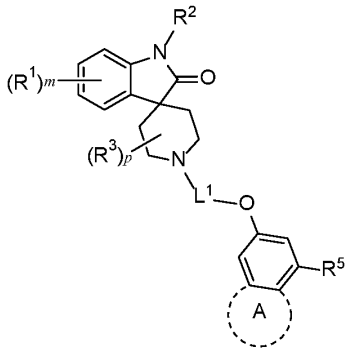


moiety represented by , has a stereochemical configuration represented by



. In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0351] In some embodiments, provided herein is a compound of formula (I), (I-A) or (I-A2), (I-E), or (I-E1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-F):

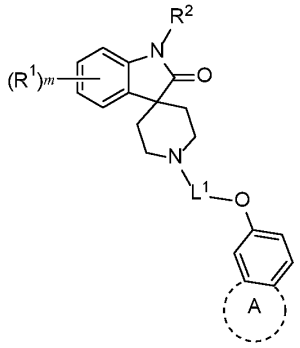


(I-F),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein: ring A is 5-10 membered heterocyclyl or a 5-10 membered heteroaryl, wherein the 5-10 membered heterocyclyl of ring A is optionally substituted with one or more R^b, and wherein the 5-10 membered heteroaryl of ring A is optionally substituted with one or more R^c; and m, p, R^1, R^2, R^3, L^1, R^5, R^b, and R^c, are as defined for formula (I). In some variations, ring A is 5-10 membered heterocyclyl or a 5-10 membered heteroaryl, wherein the 5-10 membered heterocyclyl of ring A is optionally substituted with one or more R^b, and wherein the 5-10 membered heteroaryl of ring A is

optionally substituted with one or more R^c; and *m*, *p*, R^1, R^2, R^3, L^1, R^5, R^b, and R^c of formula (I-F) are as defined for a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0352] In some embodiments, provided herein is a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), or (I-F), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-F1):



(I-F1),

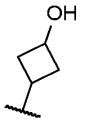
or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein: ring A is 5-10 membered heterocyclyl or a 5-10 membered heteroaryl, wherein the 5-10 membered heterocyclyl of ring A is optionally substituted with one or more R^b, and wherein the 5-10 membered heteroaryl of ring A is optionally substituted with one or more R^c; and *m*, R^1, R^2, L^1, R^b, and R^c, are as defined for formula (I). In some variations, ring A is 5-10 membered heterocyclyl or a 5-10 membered heteroaryl, wherein the 5-10 membered heterocyclyl of ring A is optionally substituted with one or more R^b, and wherein the 5-10 membered heteroaryl of ring A is optionally substituted with one or more R^c; and *m*, R^1, R^2, L^1, R^b, and R^c of formula (I-F1) are as defined for a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0353] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is H. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0354] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more -OH, $-NH_2$, or C_{1-6}alkoxy. In some embodiments, R^2 is methyl. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0355] In some embodiments of a compound of formula (II), such as a compound of formula (I'), (I), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more deuterium, -OH, $-NH_2$, or C_{1-6}alkoxy. In some embodiments, R^2 is methyl optionally substituted with one or more deuterium. In some embodiments, R^2 is 

.

[0356] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more -OH. In some embodiments, R^2 is C_{3-6}cycloalkyl, wherein the C_{3-6}cycloalkyl of R^2 is optionally substituted with one or more -OH. In some embodiments, R^2 is 

. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0357] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, *m* is an integer from 0 to 4. In some embodiments, *m* is an integer from 0 to 2. In some embodiments, *m* is 0 or 1. In some embodiments, *m* is 0. In some embodiments *m* is 1. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a

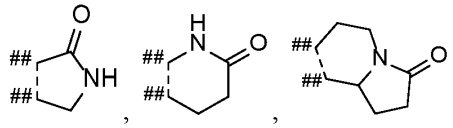
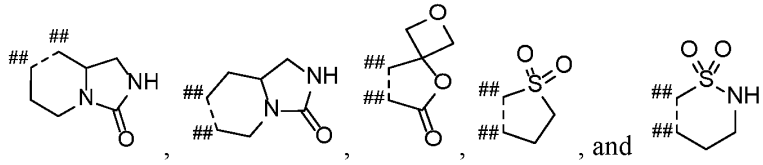
stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

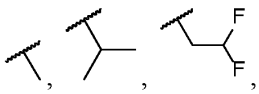
[0358] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is halo. In some embodiments R^1 is Cl. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

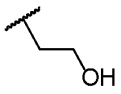
[0359] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is -CN. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof. In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1 is $C_{1\text{-}6}$alkylene, wherein the $C_{1\text{-}6}$alkylene of L^1 is optionally substituted with one or more $C_{1\text{-}6}$alkyl. In some embodiments, L^1 is ethylene, wherein the ethylene of L^1 is optionally substituted with one or more $C_{1\text{-}6}$alkyl. In some embodiments, L^1 is selected from the group consisting of  ,  , and  , wherein, for each L^1, # denotes the point of attachment to -O- and ## denotes the point of attachment to the remainder of the molecule. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

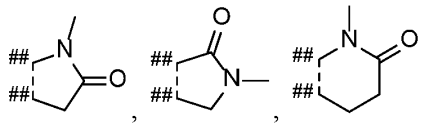
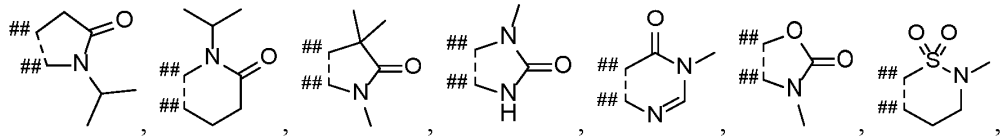
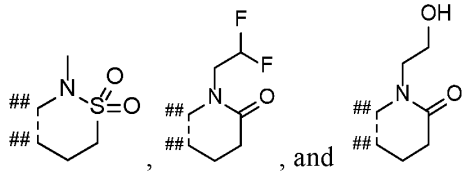
[0360] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more of R^b, wherein R^b is oxo. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more of R^b, wherein R^b is oxo. In some variations, the embodiments provided herein also

apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

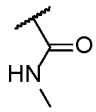
[0361] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is selected from the group consisting of  ,  , and , wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0362] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E1), (I-E2), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein each R^b is independently oxo, or C_{1-6}alkyl. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein each R^b is independently oxo, or C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^b is optionally substituted with one or more more halo, OH , or -$S(O)_2$-C_{1-6}alkyl. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein wherein each R^b is independently oxo, or C_{1-3}alkyl, wherein the C_{1-3}alkyl of R^b is optionally substituted with one or more more halo, -OH, or -$S(O)_2$-C_{1-3}alkyl. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein each R^b is independently selected from the group consisting of oxo,  ,

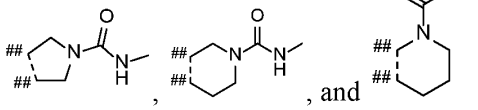
and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0363] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E1), (I-E2), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is selected from the group consisting of  ,  ,  , and , wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0364] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E1), (I-E2), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein one or more of R^b is -C(O)-NH(C_{1-6}alkyl). In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein one or more of R^b is -C(O)-NH(C_{1-3}alkyl). In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein one or more of R^b is

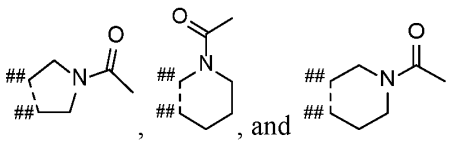


. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

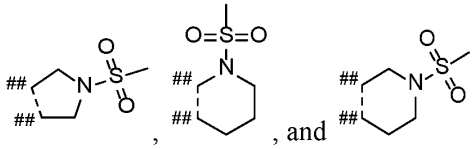
[0365] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E1), (I-E2), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is selected from the group consisting of  , wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0366] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E1), (I-E2), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein one or more of R^b is -C(O)-C_{1-6}alkyl. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein one or more of R^b is -C(O)-C_{1-3}alkyl. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein one or more of R^b is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

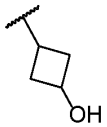
[0367] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E1), (I-E2), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the

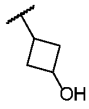
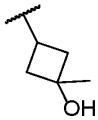
foregoing, ring A is selected from the group consisting of  , wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

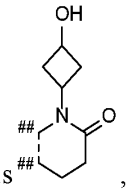
[0368] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E1), (I-E2), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein one or more of R^b is $-S(O)_2-R^a$, wherein R^a is C_{1-6}alkyl. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein one or more of R^b is $-S(O)_2-R^a$, wherein R^a is C_{1-3}alkyl. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein one or more of R^b is $-S(O)_2-R^a$, wherein R^a is methyl. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

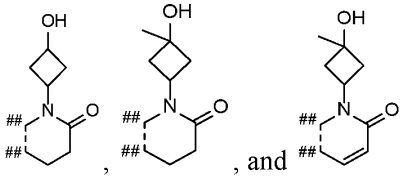
[0369] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E1), (I-E2), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is selected from the group consisting of  , wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0370] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E1), (I-E2), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the

foregoing, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more -OH. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is C_{3-6}cycloalkyl, wherein the C_{3-6}cycloalkyl of R^b is optionally substituted with one or more -OH. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein one or more of R^b is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

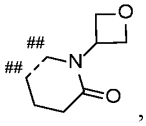
[0371] In some embodiments of a compound of formula (I'), (I-A) or (I-A2), (I-E1), (I-E2), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more -OH or C_{1-6}alkyl. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is C_{3-6}cycloalkyl, wherein the C_{3-6}cycloalkyl of R^b is optionally substituted with one or more -OH or C_{1-3}alkyl. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein one or more of R^b is selected from the group consisting of  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0372] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E1), (I-E2), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is  , wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

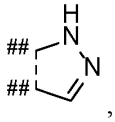
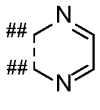
[0373] In some embodiments of a compound of formula (I'), (I-A) or (I-A2), (I-E1), (I-E2), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is selected from the group consisting of  , wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond. In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0374] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E1), (I-E2), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is 3-10 membered heterocyclyl. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is 3-6 membered heterocyclyl. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein one or more of R^b is  . In some variations,

the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

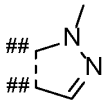
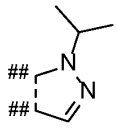
[0375] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E1), (I-E2), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is  , wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0376] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E1), (I-E2), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is a 5-10 membered heteroaryl. In some embodiments, ring A is a 5-6 membered heteroaryl. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0377] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E1), (I-E2), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is selected from the group consisting of  , and  , wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

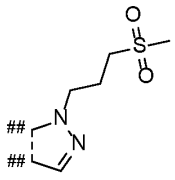
[0378] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is a 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl is optionally substituted with one or more R^c,

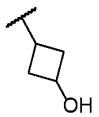
wherein one or more R^c is C_{1-6}alkyl. In some embodiments ring A is a 5-6 membered heteroaryl, wherein the 5-6 membered heteroaryl is optionally substituted with one or more R^c, wherein one or more R^c is C_{1-3}alkyl. In some embodiments, ring A is a 5-6 membered heteroaryl, wherein the 5-6 membered heteroaryl is optionally substituted with one or more R^c, wherein one or more R^c is methyl. In some embodiments, ring A is a 5-6 membered heteroaryl, wherein the 5-6 membered heteroaryl is optionally substituted with one or more R^c, wherein one or more R^c is isopropyl. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0379] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E1), (I-E2), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is selected from the group consisting of  , and  , wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

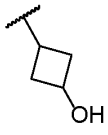
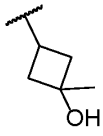
[0380] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E1), (I-E2), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is a 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl is optionally substituted with one or more R^c, wherein one or more R^c is C_{1-6}alkyl, wherein the C_{1-6} alkyl of R^c is optionally substituted with one or more $-S(O)_2-R^a$, wherein R^a is C_{1-6}alkyl. In some embodiments, ring A is a 5-6 membered heteroaryl, wherein the 5-6 membered heteroaryl is optionally substituted with one or more R^c, wherein one or more R^c is C_{1-3}alkyl, wherein the C_{1-3}alkyl of R^c is optionally substituted with one or more $-S(O)_2-R^a$, wherein R^a is C_{1-3}alkyl. In some embodiments, ring A is a 5-6 membered heteroaryl, wherein the 5-6 membered heteroaryl is optionally substituted with one or more R^c, wherein one or more R^c is C_{1-3}alkyl, wherein the C_{1-3}alkyl of R^c is optionally substituted with one or more $-S(O)_2-R^a$, wherein R^a is methyl. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a

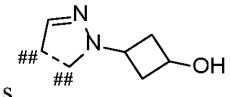
stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

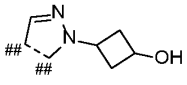
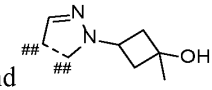
[0381] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E1), (I-E2), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is  , wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0382] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E1), (I-E2), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is a 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl is optionally substituted with one or more R^c, wherein one or more R^c is C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of R^c is optionally substituted with one or more -OH. In some embodiments, ring A is a 5-10 membered heteroaryl, wherein the 5-6 membered heteroaryl is optionally substituted with one or more R^c, wherein one or more R^c is C_{3-6}cycloalkyl, wherein the C_{3-6}cycloalkyl of R^c is optionally substituted with one or more -OH. In some embodiments, ring A is a 5-10 membered heteroaryl, wherein the 5-6 membered heteroaryl is optionally substituted with one or more R^c, wherein one or more R^c is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

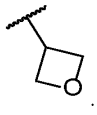
[0383] In some embodiments of a compound of formula (I'), (I-A) or (I-A2), (I-E1), (I-E2), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is a 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl is optionally substituted with one or more R^c, wherein one or more R^c is C_{3-10}cycloalkyl, wherein the

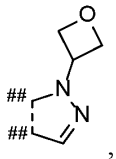
C_{3-10}cycloalkyl of R^c is optionally substituted with one or more -OH, or C_{1-6}alkyl. In some embodiments, ring A is a 5-10 membered heteroaryl, wherein the 5-6 membered heteroaryl is optionally substituted with one or more R^c, wherein one or more R^c is C_{3-6}cycloalkyl, wherein the C_{3-6}cycloalkyl of R^c is optionally substituted with one or more -OH, or C_{1-3}alkyl. In some embodiments, ring A is a 5-10 membered heteroaryl, wherein the 5-6 membered heteroaryl is optionally substituted with one or more R^c, wherein one or more R^c is selected from the group consisting of  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0384] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E1), (I-E2), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is  , wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

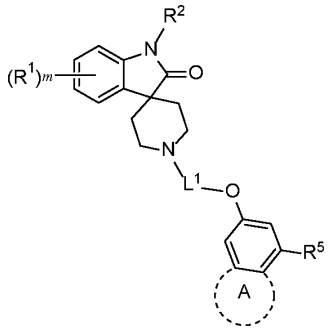
[0385] In some embodiments of a compound of formula (I'), (I-A) or (I-A2), (I-E1), (I-E2), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is selected from the group consisting of  , and  , wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond. In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0386] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E1), (I-E2), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the

foregoing, ring A is a 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl is optionally substituted with one or more R^b, wherein R^b is 3-10 membered heterocyclyl. In some embodiments, ring A is a 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl is optionally substituted with one or more R^b, wherein R^b is 3-6 membered heterocyclyl. In some embodiments, ring A is a 5-10 membered heteroaryl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein one or more of R^b is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0387] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E1), (I-E2), (I-F), or (I-F1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is  , wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0388] In some embodiments, provided herein is a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), or (I-F), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-F2):



(I-F2),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein: R^5 is halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH and wherein the C_{1-6}alkoxy is optionally substituted with one or more halo; ring A is 5-10 membered heterocyclyl or a 5-10 membered heteroaryl, wherein the 5-10 membered heterocyclyl of ring A is optionally substituted with one or more R^b, and wherein the 5-10 membered heteroaryl of ring A is optionally substituted with one or more R^c; and *m*, R^1, R^2, L^1, R^b, and R^c, are as defined for formula (I). In some variations, R^5 is halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH and wherein the C_{1-6}alkoxy of R^5 is optionally substituted with one or more halo; ring A is 5-10 membered heterocyclyl or a 5-10 membered heteroaryl, wherein the 5-10 membered heterocyclyl of ring A is optionally substituted with one or more R^b, and wherein the 5-10 membered heteroaryl of ring A is optionally substituted with one or more R^c; and *m*, R^1, R^2, L^1, R^b, and R^c, of formula (I-F2) are as defined for a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0389] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is H. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0390] In some embodiments of a compound of formula (II), such as a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F2), or a stereoisomer or tautomer thereof, or a

pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more deuterium, -OH, $-NH_2$, or C_{1-6}alkoxy. In some embodiments, R^2 is methyl optionally substituted with one or more deuterium. In some embodiments, R^2 is  .

[0391] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, *m* is an integer from 0 to 4. In some embodiments, *m* is an integer from 0 to 2. In some embodiments *m* is 1. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0392] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is halo. In some embodiments R^1 is Cl. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0393] In some embodiments of a compound of formula (II), such as a compound of formula (I'), (I), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is halo. In some embodiments R^1 is Cl, Br, or I.

[0394] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is -CN. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

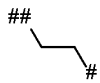
[0395] In some embodiments of a compound of formula (II), such as a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^1 is optionally substituted with one or more halo. In some embodiments, R^1 is C_{1-3}alkyl, wherein the

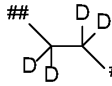
C_{1-3}alkyl of R^1 is optionally substituted with one or more halo. In some embodiments, R^1 is C_{1-3}alkyl, wherein the C_{1-3}alkyl of R^1 is optionally substituted with one or more F. In some embodiments, R^1 is methyl, wherein the methyl of R^1 is optionally substituted with one or more F. In some embodiments, R^1 is 

.

[0396] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1 is C_{1-6}alkylene. In some embodiments, L^1 is ethylene. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof. In some embodiments, L^1 is 

, wherein, for each L^1, # denotes the point of attachment to L^2 and ## denotes the point of attachment to the remainder of the molecule. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

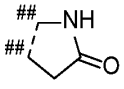
[0397] In some embodiments of a compound of formula (II), such as a compound of formula (I'), (I), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1 is C_{1-6}alkylene, optionally substituted with one or more deuterium. In some embodiments, L^1 is ethylene optionally substituted with one or more deuterium. In some embodiments, L^1 is 

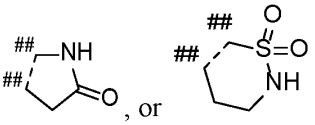
, or 

wherein, for each L^1, # denotes the point of attachment to L^2 and ## denotes the point of attachment to the remainder of the molecule.

[0398] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more of R^b, wherein one or more R^b is oxo. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally

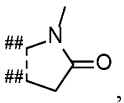
substituted with one or more of R^b, wherein one or more R^b is oxo. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

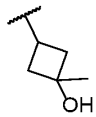
[0399] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is  , wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

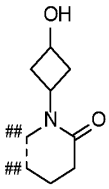
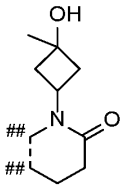
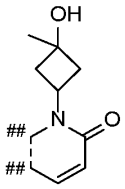
[0400] In some embodiments of a compound of formula (II), such as a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is  , or , wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond.

[0401] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein each R^b is independently oxo, or C_{1-6}alkyl. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein each R^b is independently oxo, or C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^b is optionally substituted with one or more more halo, OH , or -$S(O)_2$-C_{1-6}alkyl. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein each R^b is independently oxo, or C_{1-3}alkyl. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein each

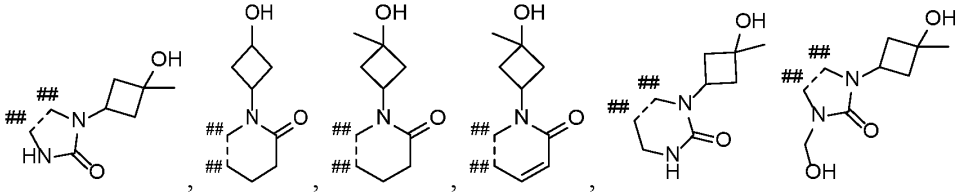
R^b is independently selected from the group consisting of oxo, and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

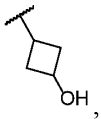
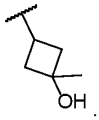
[0402] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is  , wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

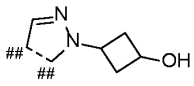
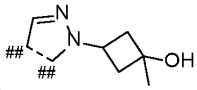
[0403] In some embodiments of a compound of formula (I'), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more -OH or C_{1-6}alkyl. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is C_{3-6}cycloalkyl, wherein the C_{3-6}cycloalkyl of R^b is optionally substituted with one or more -OH or C_{1-3}alkyl. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein one or more of R^b is selected from the group consisting of  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

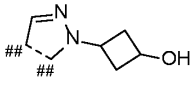
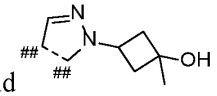
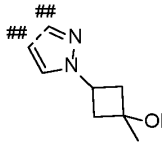
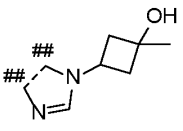
[0404] In some embodiments of a compound of formula (I'), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is selected from the group consisting of  ,  , and  , wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond. In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

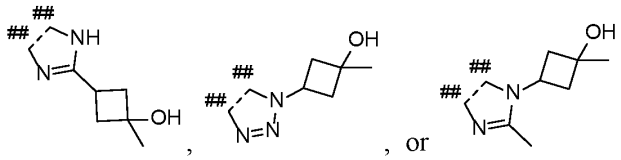
[0405] In some embodiments of a compound of formula (II), such as a compound of formula (I'), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is C_{1-6}alkyl and wherein, the C_{1-6}alkyl of R^b is optionally substituted with one or more -OH. In some embodiments, ring A is 5-6 membered heterocyclyl, wherein the 5-6 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is C_{1-3}alkyl and wherein, the C_{1-3}alkyl of R^b is optionally substituted with one or more -OH. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-6 membered heterocyclyl is optionally substituted with one or more R^b, wherein one or more of R^b is $-CH_2OH$.

[0406] In some embodiments of a compound of formula (II), such as a compound of formula (I'), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is selected from the group consisting of  , wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond.

[0407] In some embodiments of a compound of formula (I'), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is a 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl is optionally substituted with one or more R^c, wherein one or more R^c is C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of R^c is optionally substituted with one or more -OH, or C_{1-6}alkyl. In some embodiments, ring A is a 5-10 membered heteroaryl, wherein the 5-6 membered heteroaryl is optionally substituted with one or more R^c, wherein one or more R^c is C_{3-6}cycloalkyl, wherein the C_{3-6}cycloalkyl of R^c is optionally substituted with one or more -OH, or C_{1-3}alkyl. In some embodiments, ring A is a 5-10 membered heteroaryl, wherein the 5-6 membered heteroaryl is optionally substituted with one or more R^c, wherein one or more R^c is selected from the group consisting of  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0408] In some embodiments of a compound of formula (I'), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is selected from the group consisting of  , and  , wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond. In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0409] In some embodiments of a compound of formula (II), such as a compound of formula (I'), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is selected from the group consisting of  , and  ,  ,  ,



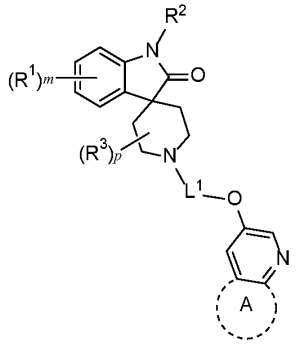
. wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond.

[0410] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^5 is halo. In some embodiments, R^5 is fluoro. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0411] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^5 is C_{1-6}alkyl. In some embodiments, R^5 is C_{1-3}alkyl. In some embodiments, R^5 is methyl. In some embodiments, R^5 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo. In some embodiments, R^5 is C_{1-3}alkyl, wherein the C_{1-3}alkyl of R^5 is optionally substituted with one or more halo. In some embodiments, R^5 is C_{1-3}alkyl, wherein the C_{1-3}alkyl of R^5 is optionally substituted with one or more fluoro. In some embodiments, R^5 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0412] In some embodiments of a compound of formula (II), such as a compound of formula (I'), (I-A) or (I-A2), (I-E), (I-E1), (I-F), or (I-F2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^5 is halo, -CN, or C_{1-6}alkoxy, wherein the C_{1-6}alkoxy of R^5 is optionally substituted with one or more halo. In some embodiments, R^5 F, -CN, or C_{1-3}alkoxy, wherein the C_{1-3}alkoxy of R^5 is optionally substituted with one or more F. In some embodiments, R^5 is $-OCHF_2$.

[0413] In some embodiments, provided herein is a compound of formula (I), (I-A) or (I-A2), (I-E1), or (I-E2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-G):



(I-G),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein: ring A is 5-10 membered heterocyclyl or a 5-10 membered heteroaryl, wherein the 5-10 membered heterocyclyl of ring A is optionally substituted with one or more R^b, and wherein the 5-10 membered heteroaryl of ring A is optionally substituted with one or more R^c; and *m*, R^1, R^2, L^1, R^b, and R^c, are as defined for formula (I). In some variations, ring A is 5-10 membered heterocyclyl or a 5-10 membered heteroaryl, wherein the 5-10 membered heterocyclyl of ring A is optionally substituted with one or more R^b, and wherein the 5-10 membered heteroaryl of ring A is optionally substituted with one or more R^c; and *m*, R^1, R^2, L^1, R^b, and R^c of formula (I-G) are as defined for a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0414] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), or (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is H. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0415] In some embodiments of a compound of formula (II), such as a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), or (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is $C_{1\text{-}6}$alkyl, wherein the $C_{1\text{-}6}$alkyl of R^2 is optionally

substituted with one or more deuterium. In some embodiments, R^2 is methyl optionally substituted with one or more deuterium. In some embodiments, R^2 is  .

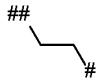
[0416] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), or (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, *m* is an integer from 0 to 4. In some embodiments, *m* is an integer from 0 to 2. In some embodiments, *m* is 0 or 1. In some embodiments *m* is 1. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0417] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), or (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is halo. In some embodiments R^1 is Cl. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0418] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), or (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is -CN. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

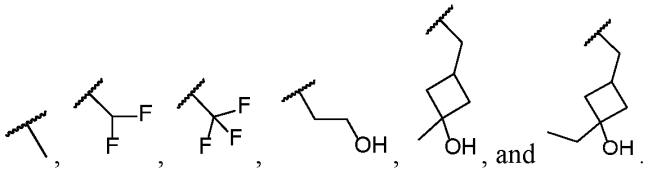
[0419] In some embodiments of a compound of formula (I'), (I-A) or (I-A2), (I-E), (I-E1), or (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^1 is optionally substituted with one or more halo. In some embodiments, R^1 is C_{1-3}alkyl, wherein the C_{1-3}alkyl of R^1 is optionally substituted with one or more halo. In some embodiments, R^1 is C_{1-3}alkyl, wherein the C_{1-3}alkyl of R^1 is optionally substituted with one or more F. In some embodiments, R^1 is methyl, wherein the methyl of R^1 is optionally substituted with one or more F. In some embodiments, R^1 is methyl. In some embodiments, R^1 is  . In some variations, the embodiments provided herein also apply to a

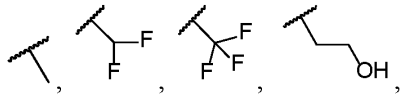
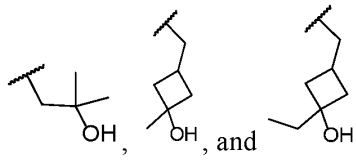
compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

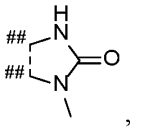
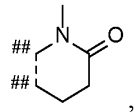
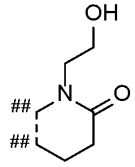
[0420] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), or (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1 is C_{1-6}alkylene. In some embodiments, L^1 is C_{1-3}alkylene. In some embodiments, L^1 is ethylene. In some embodiments, L^1 is  , wherein, for each L^1, # denotes the point of attachment to -O- and ## denotes the point of attachment to the remainder of the molecule. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

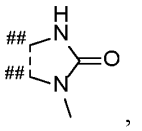
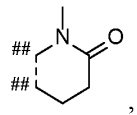
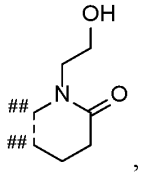
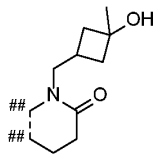
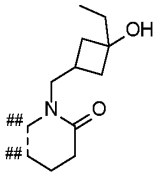
[0421] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), or (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein each R^b is independently oxo, or C_{1-6}alkyl. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein each R^b is independently oxo, or C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^b is optionally substituted with one or more -OH. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein wherein each R^b is independently oxo, or C_{1-3}alkyl, wherein the C_{1-3}alkyl of R^b is optionally substituted with one or more -OH. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein each R^b is independently selected from the group consisting of oxo,  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0422] In some embodiments of a compound of formula (I'), (I-A) or (I-A2), (I-E), (I-E1), or (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the

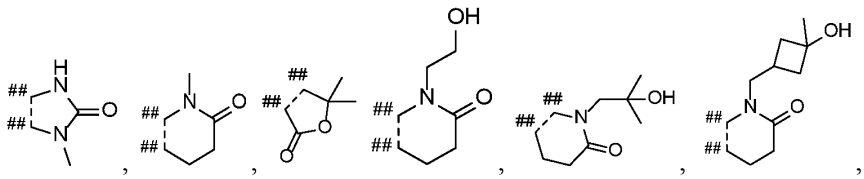
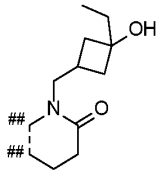
foregoing, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein each R^b is independently oxo, or C_{1-6}alkyl. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein each R^b is independently oxo, or C_{1-6}alkyl. In some embodiments, the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, OH, $-S(O)_2-C_{1-6}$alkyl, or C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of the C_{1-6}alkyl of R^b is further optionally substituted with one or more C_{1-6}alkyl or -OH. In some embodiments, each R^b is independently oxo, or C_{1-3}alkyl. In some embodiments the C_{1-3}alkyl of R^b is optionally substituted with one or more halo, OH, $-S(O)_2-C_{1-3}$alkyl, or C_{3-6}cycloalkyl, wherein the C_{3-6}cycloalkyl of the C_{1-3}alkyl of R^b is further optionally substituted with one or more C_{1-3}alkyl or -OH. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein each R^b is independently selected from the group consisting of oxo,  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0423] In some embodiments of a compound of formula (II), such as a compound of formula (I'), (I-A) or (I-A2), (I-E), (I-E1), or (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein each R^b is independently selected from the group consisting of oxo,  ,  .

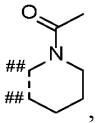
[0424] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), or (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is selected from the group consisting of  ,  , and  , wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

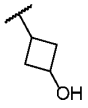
[0425] In some embodiments of a compound of formula (I'), (I-A) or (I-A2), (I-E), (I-E1), or (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is selected from the group consisting of  ,  ,  ,  , and  wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond. In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

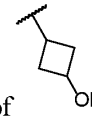
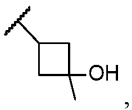
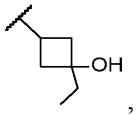
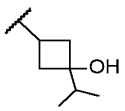
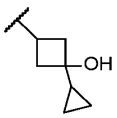
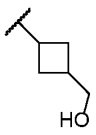
[0426] In some embodiments of a compound of formula (II), such as a compound of formula (I'), (I-A) or (I-A2), (I-E), (I-E1), or (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is selected from the group

consisting of  , and  wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond.

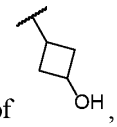
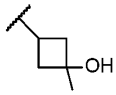
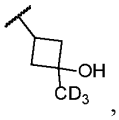
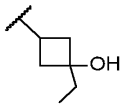
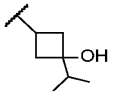
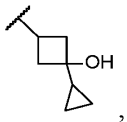
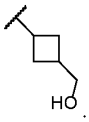
[0427] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), or (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein one or more of R^b is -C(O)-C_{1-6}alkyl. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein one or more of R^b is -C(O)-C_{1-3}alkyl. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein one or more of R^b is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

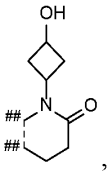
[0428] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), or (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is  , wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

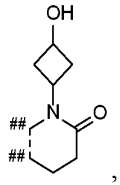
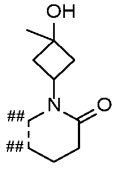
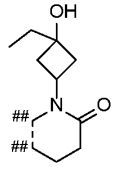
[0429] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), or (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more –OH. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is C_{3-6}cycloalkyl, wherein the C_{3-6}cycloalkyl of R^b is optionally substituted with one or more -OH. In some embodiments, ring A is a 5-10 membered heterocyclyl, wherein the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein one or more of R^b is  . In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

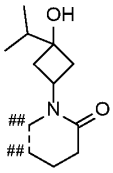
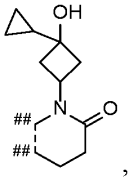
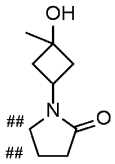
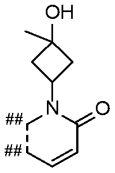
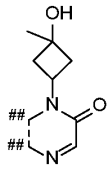
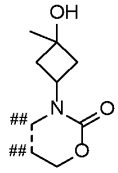
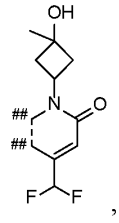
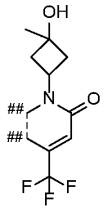
[0430] In some embodiments of a compound of formula (I'), (I-A) or (I-A2), (I-E), (I-E1), or (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^b is C_{3-10}cycloalkyl optionally substituted with one or more -OH, C_{3-10}cycloalkyl, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is further optionally substituted with one or more -OH. In some embodiments, R^b is C_{3-6}cycloalkyl optionally substituted with one or more -OH, C_{3-6}cycloalkyl, or C_{1-3}alkyl, wherein the C_{1-3}alkyl is further optionally substituted with one or more –OH. In some embodiments, R^b is selected from the group consisting of  ,  ,  ,  ,  , and  . In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

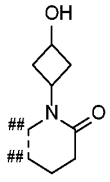
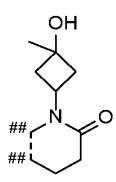
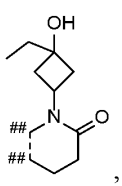
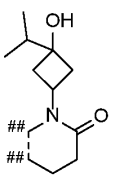
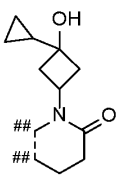
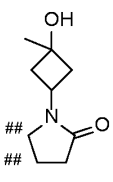
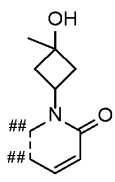
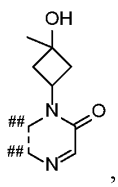
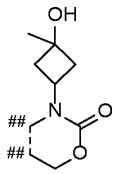
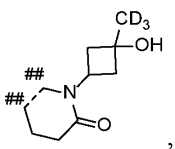
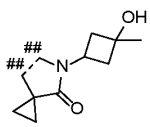
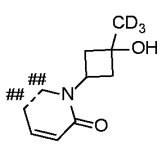
[0431] In some embodiments of a compound of formula (II), such as a compound of formula (I'), (I-A) or (I-A2), (I-E), (I-E1), or (I-G), or a stereoisomer or tautomer thereof, or a

pharmaceutically acceptable salt of any of the foregoing, R^b is C_{3-10}cycloalkyl optionally substituted with one or more -OH, C_{3-10}cycloalkyl, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is further optionally substituted with one or more -OH or deuterium. In some embodiments, R^b is C_{3-6}cycloalkyl optionally substituted with one or more -OH, C_{3-6}cycloalkyl, or C_{1-3}alkyl, wherein the C_{1-3}alkyl is further optionally substituted with one or more -OH or deuterium. In some embodiments, R^b is selected from the group consisting of  ,  ,  ,  ,  ,  , and  .

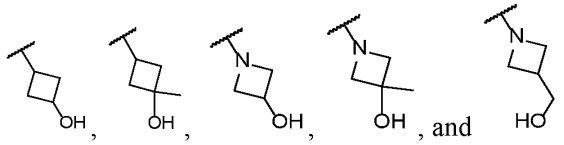
[0432] In some embodiments of a compound of formula (I), (I-A) or (I-A2), (I-E), (I-E1), or (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is  , wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond. In some variations, the embodiments provided herein also apply to a compound of formula (I'), or (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0433] In some embodiments of a compound of formula (I'), (I-A) or (I-A2), (I-E), (I-E1), or (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is selected from the group consisting of  ,  ,  ,






, and  wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond. In some embodiments, ring A is selected from the group consisting of  , and  , wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond. In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

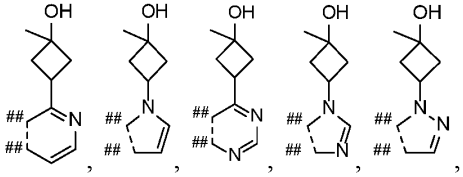
[0434] In some embodiments of a compound of formula (II), such as a compound of formula (I'), (I-A) or (I-A2), (I-E), (I-E1), or (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is selected from the group consisting 










, and  wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond.

[0435] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^c is independently at each occurrence, selected from the group consisting of halo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -S(O)$_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein the C_{1-6}alkyl of R^c is optionally substituted with one or more -S(O)$_2$-C_{1-6}alkyl, the C_{3-10}cycloalkyl of R^c is optionally substituted with one or more –OH, or C_{1-6}alkyl, and the 3-10 membered heterocyclyl of R^c is optionally substituted with one or more -OH, or C_{1-6}alkyl,wherein the C_{1-6}alkyl is further optionally substituted with one or more -OH. In some embodiments, R^c is independently at each occurrence, selected from the group consisting of halo, C_{1-3}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-3}alkyl), -C(O)-N(C_{1-3}alkyl)$_2$, -S(O)$_2$-R^a, C_{3-6}cycloalkyl, and 3-6 membered heterocyclyl, wherein the C_{1-3}alkyl of R^c is optionally substituted with one or more -S(O)$_2$-C_{1-3}alkyl, the C_{3-6}cycloalkyl of R^c is optionally substituted with one or more –OH, or C_{1-3}alkyl, and the 3-6 membered heterocyclyl of R^c is optionally substituted with one or more -OH, or C_{1-3}alkyl,wherein the C_{1-3}alkyl is further optionally substituted with one or more -OH. In some embodiments, R^c is selected from the group consisting of methyl, isopropyl, –S(O)$_2$CH$_3$, and

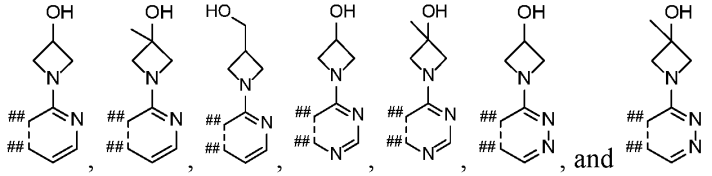


. In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0436] In some embodiments of a compound of formula (I'), (I-A) or (I-A2), (I-E), (I-E1), or (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is selected from the group consisting of



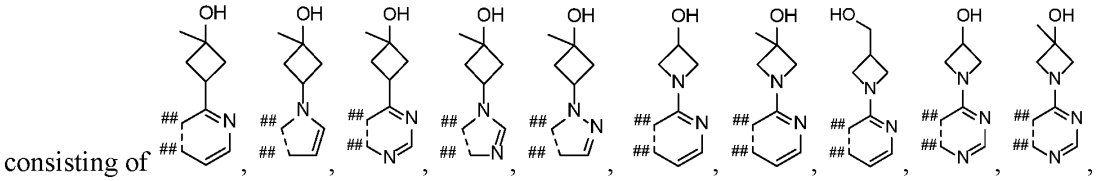
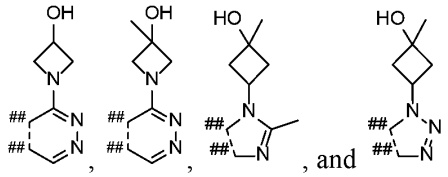
,



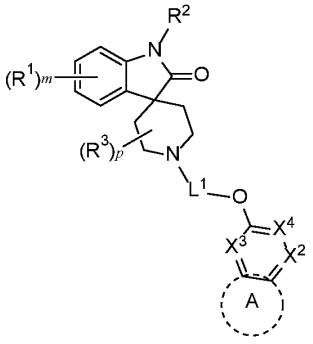
, and

wherein ## represent a point of

attachment to the remainder of the molecule and the dashed line represents a single or double bond. In some variations, the embodiments provided herein also apply to a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0437] In some embodiments of a compound of formula (II), such as a compound of formula (I'), (I-A) or (I-A2), (I-E), (I-E1), or (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is selected from the group consisting of  ,  , and wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond.

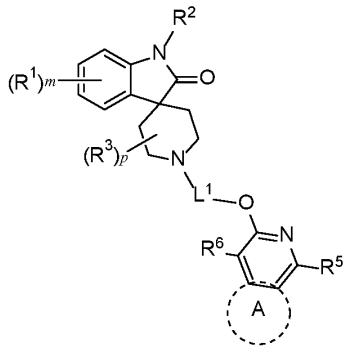
[0438] In some embodiments, provided herein is a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (II-A):


(II-A),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein: ring A is 5-10 membered heterocyclyl or a 5-10 membered heteroaryl, wherein the 5-10 membered heterocyclyl of ring A is optionally substituted with one or more R^b, and wherein the 5-

10 membered heteroaryl of ring A is optionally substituted with one or more R^c; and m, p, R^1, R^2, R^3, L^1, R^b, R^c, X^2, X^3, and X^4 are as defined for formula (II).

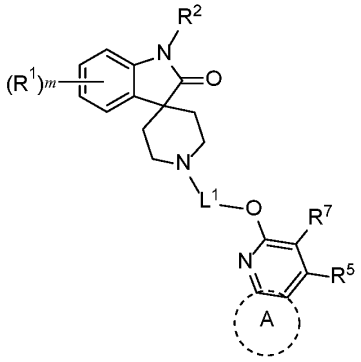
[0439] In some embodiments, provided herein is a compound of formula (II), or (II-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (II-A1):



(II-A1),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein: ring A is 5-10 membered heterocyclyl or a 5-10 membered heteroaryl, wherein the 5-10 membered heterocyclyl of ring A is optionally substituted with one or more R^b, and wherein the 5-10 membered heteroaryl of ring A is optionally substituted with one or more R^c; and m, R^1, R^2, R^6, L^1, R^b, and R^c are as defined for formula (II).

[0440] In some embodiments, provided herein is a compound of formula (II), or (II-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (II-A2):



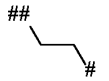
(II-A2),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein: ring A is 5-10 membered heterocyclyl or a 5-10 membered heteroaryl, wherein the 5-10 membered heterocyclyl of ring A is optionally substituted with one or more R^b, and wherein the 5-10 membered heteroaryl of ring A is optionally substituted with one or more R^c; and *m*, R^1, R^2, R^7, L^1, R^b, and R^c are as defined for formula (II).

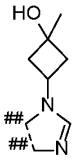
[0441] In some embodiments of a compound of formula (II), (II-A), (II-A1), or (II-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is H.

[0442] In some embodiments of a compound of formula (II), (II-A), (II-A1), or (II-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, *m* is an integer from 0 to 4. In some embodiments, *m* is an integer from 0 to 2. In some embodiments, *m* is 0 or 1. In some embodiments *m* is 1.

[0443] In some embodiments of a compound of formula (II), (II-A), (II-A1), or (II-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is halo. In some embodiments R^1 is Cl.

[0444] In some embodiments of a compound of formula (II), (II-A), (II-A1), or (II-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1 is C_{1-6}alkylene. In some embodiments, L^1 is C_{1-3}alkylene. In some embodiments, L^1 is ethylene. In some embodiments, L^1 is  , wherein, for each L^1, # denotes the point of attachment to -O- and ## denotes the point of attachment to the remainder of the molecule.

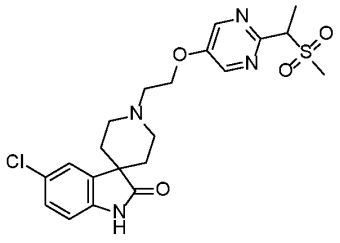
[0445] In some embodiments of a compound of formula (II), (II-A), (II-A1), or (II-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^c is independently at each occurrence C_{3-10}cycloalkyl optionally substituted with one or more -OH, or C_{1-6}alkyl. In some embodiments, R^c is independently at each occurrence, C_{3-6}cycloalkyl optionally substituted with one or more -OH, or C_{1-3}alkyl. In some embodiments, R^c is  .

[0446] In some embodiments of a compound of formula (II), (II-A), (II-A1), or (II-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is  wherein ## represent a point of attachment to the remainder of the molecule and the dashed line represents a single or double bond.

[0447] In some embodiments of a compound of formula (II), (II-A), (II-A1), or (II-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^5 is $C_{1\text{-}6}$alkyl optionally substituted with one or more halo. In some embodiments R^5 is CF_3.

[0448] In some embodiments of a compound of formula (II), (II-A), or (II-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^6 is H.

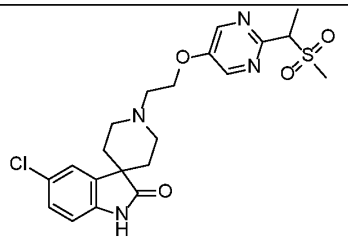
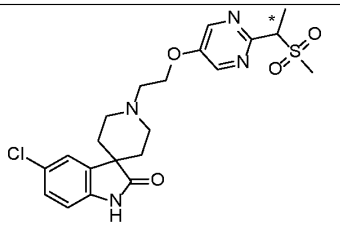
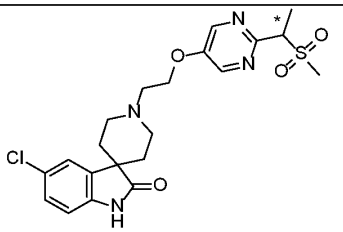
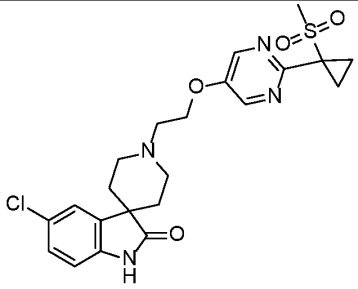
[0449] In some embodiments of a compound of formula (II), (II-A), or (II-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^7 is H.

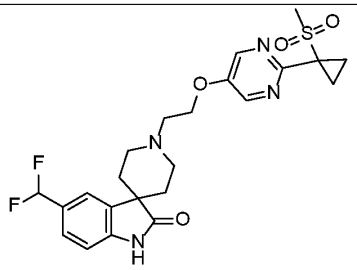
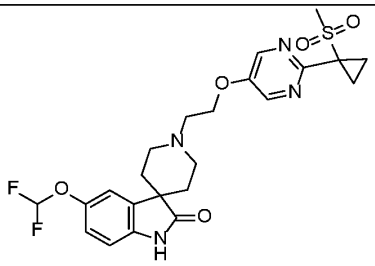
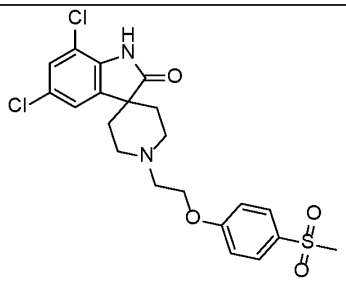
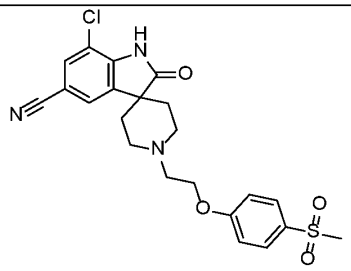
[0450] It is to be understood that any variation or embodiment of *m*, *n*, *p*, R^1, R^2, R^3, L^1, L^2 L^3, X^1, X^2, X^3, X^4, R^4, R^5, R^6, R^7, R^a, R^b, R^c, Y^1, Y^2, and Y^3 provided herein can be combined with every other variation or embodiment of *m*, *n*, *p*, R^1, R^2, R^3, L^1, L^2 L^3, X^1, X^2, X^3, X^4, R^4, R^5, R^6, R^7, R^a, R^b, R^c, Y^1, Y^2, and Y^3, the same as if each and every combination had been individually and specifically described. For example, embodiments where *m* is 1, *n* is 1, *p* is 0, R^1 is Cl, R^2 is H, L^1 is ethylene, L^2 is O, L^3 is $C_{1\text{-}6}$alkyl, R^4 is SO_2R^a wherein R^a is $C_{1\text{-}6}$alkyl, X^1 is N, X^2 is N, R^6 is H, and R^7 is H, can be combined to give  .

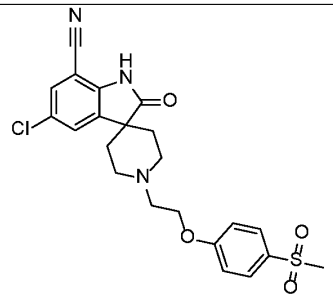
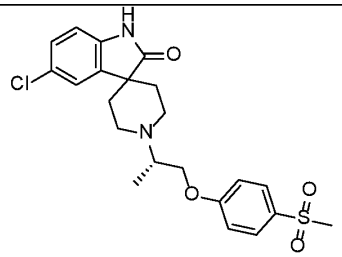
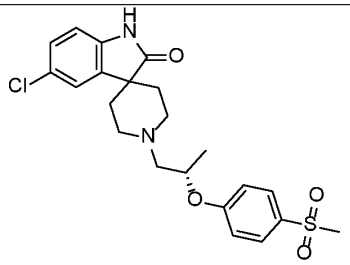
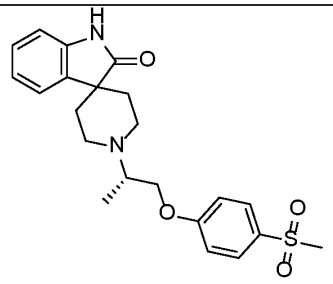
[0451] In some embodiments, provided herein is a compound of formula (I), or any variation of embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of

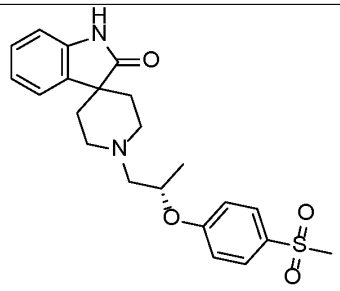
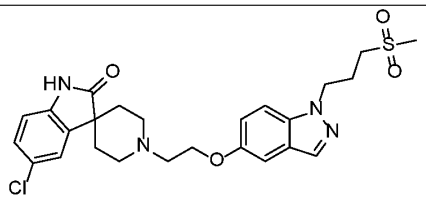
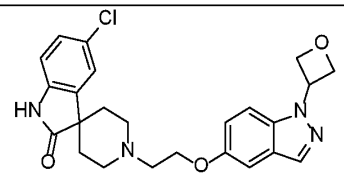
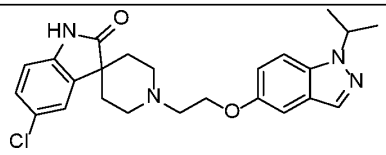
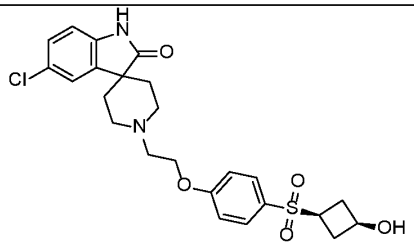
any of the foregoing, wherein the compound is a compound of Table 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

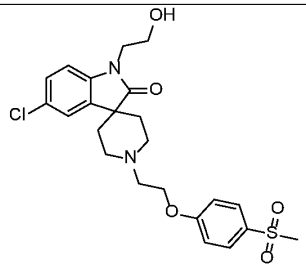
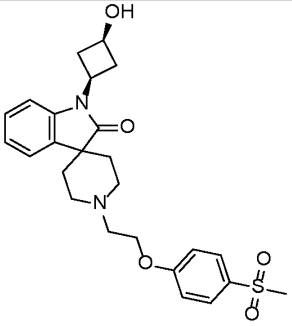
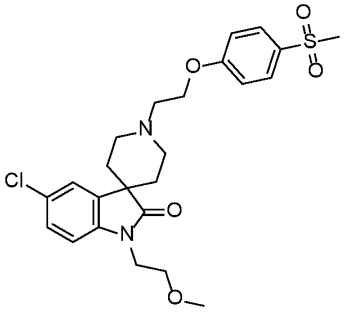
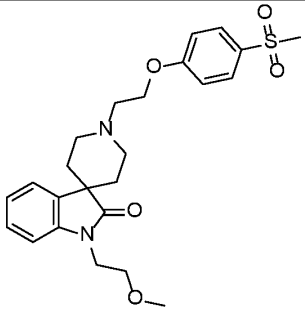
Table 1.

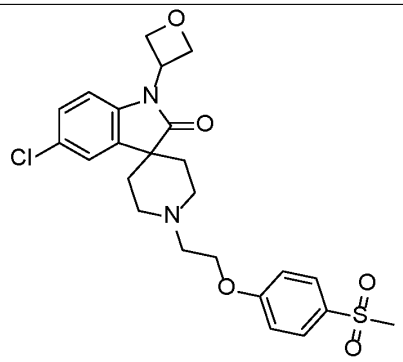
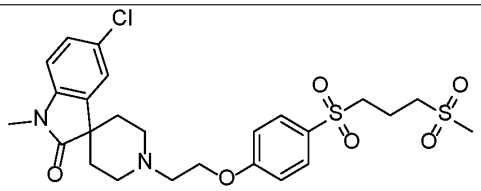
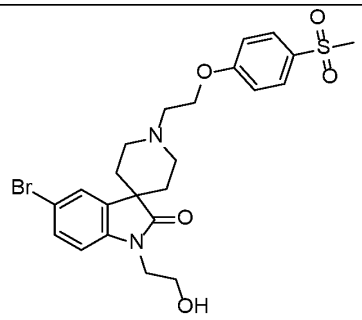
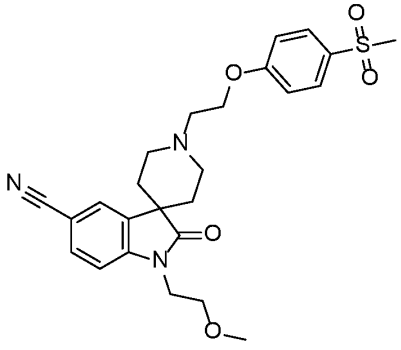
Compound Number	Structure	Name
1		5-chloro-1'-(2-{[2-(1-methanesulfonylethyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
2		5-chloro-1'-[2-({2-[(1S) or (1R)-1-methanesulfonylethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
3		5-chloro-1'-[2-({2-[(1R) or (1S)-1-methanesulfonylethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
4		5-chloro-1'-(2-{[2-(1-methanesulfonylcyclopropyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

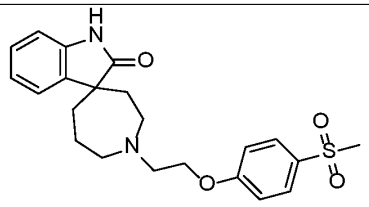
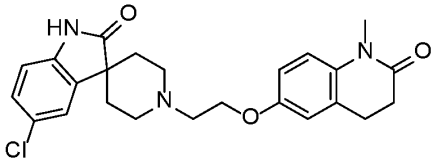
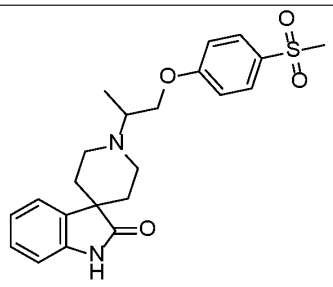
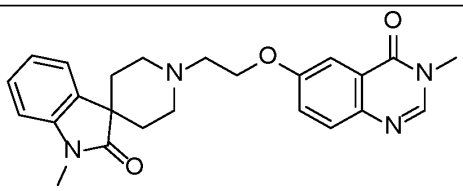
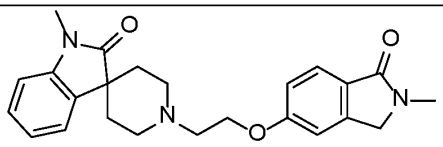
5		5-(difluoromethyl)-1'-(2-{[2-(1-methanesulfonylcyclopropyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
6		5-(difluoromethoxy)-1'-(2-{[2-(1-methanesulfonylcyclopropyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
7		5,7-dichloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
8		7-chloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile

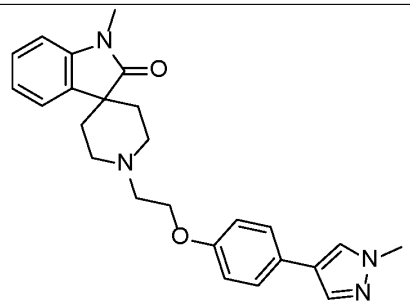
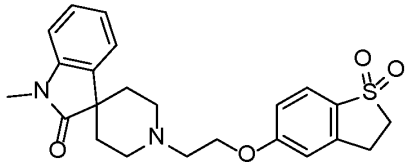
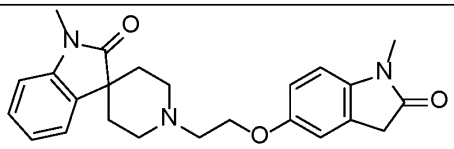
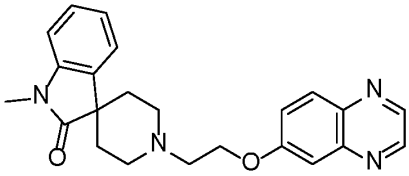
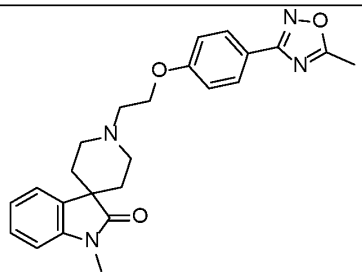
9		5-chloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-7-carbonitrile
10		5-chloro-1'-[(2S)-1-(4-methanesulfonylphenoxy)propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
11		5-chloro-1'-[(2S)-2-(4-methanesulfonylphenoxy)propyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
12		1'-[(2S)-1-(4-methanesulfonylphenoxy)propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

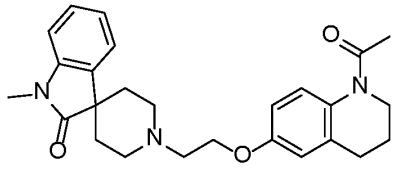
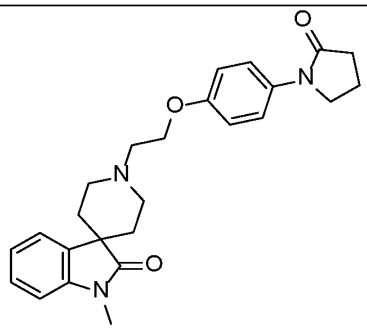
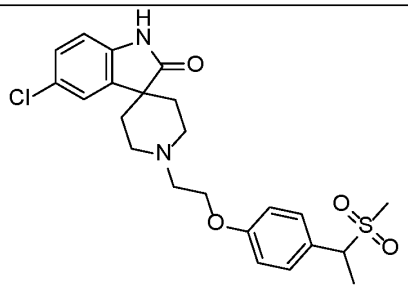
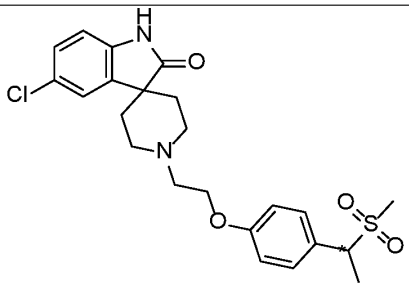
13		1'-[(2S)-2-(4-methanesulfonylphenoxy)propyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
14		5-chloro-1'-(2-{[1-(3-methanesulfonylpropyl)-1H-indazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
15		5-chloro-1'-(2-{[1-(oxetan-3-yl)-1H-indazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
16		5-chloro-1'-(2-{[1-(propan-2-yl)-1H-indazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
17		5-chloro-1'-[2-(4-{[(*cis*)-3-hydroxycyclobutyl]sulfonyl}phenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

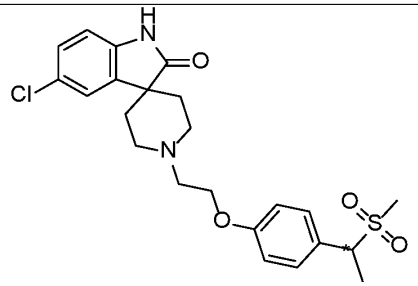
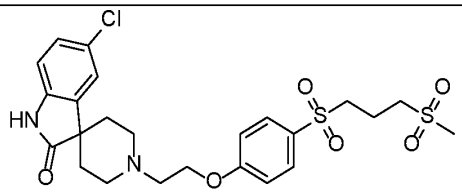
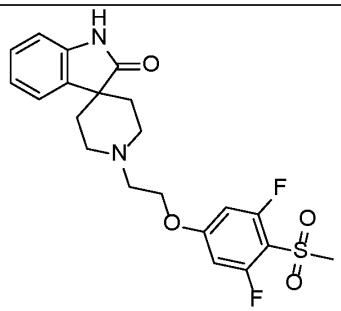
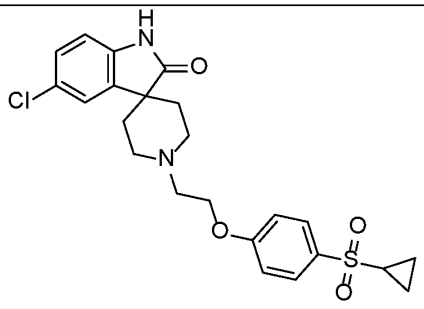
18		5-chloro-1-(2-hydroxyethyl)-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
19		1'-[2-(4-methanesulfonylphenoxy)ethyl]-1-[(*cis*)-3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
20		5-chloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1-(2-methoxyethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
21		1'-[2-(4-methanesulfonylphenoxy)ethyl]-1-(2-methoxyethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

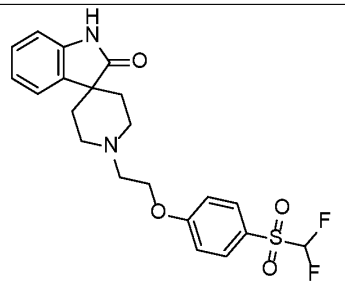
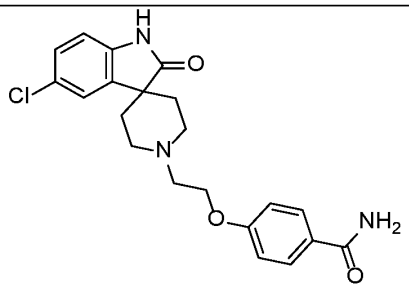
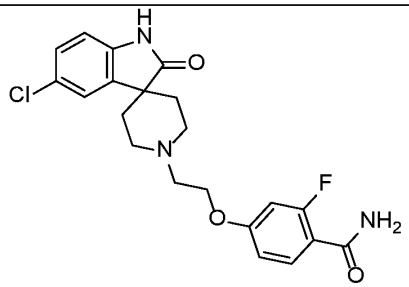
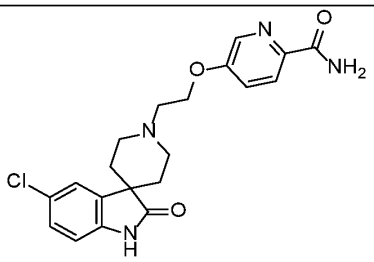
22		5-chloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1-(oxetan-3-yl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
23		5-chloro-1'-{2-[4-(3-methanesulfonylpropanesulfonyl)phenoxy]ethyl}-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
24		5-bromo-1-(2-hydroxyethyl)-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
25		1'-[2-(4-methanesulfonylphenoxy)ethyl]-1-(2-methoxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile

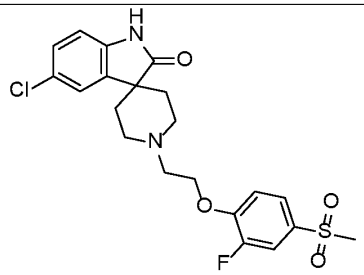
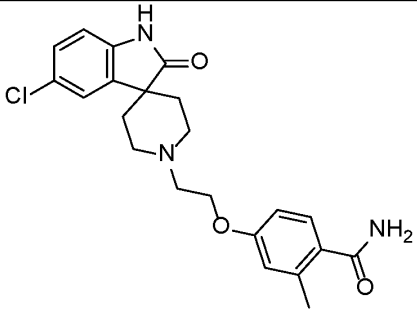
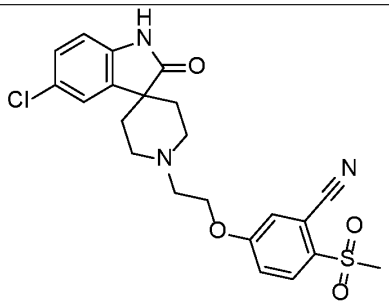
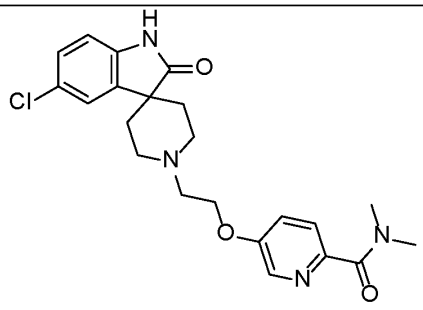
26		1-[2-(4-methanesulfonylphenoxy)ethyl]-1',2'-dihydrospiro[azepane-4,3'-indol]-2'-one
27		5-chloro-1'-{2-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
28		1'-[1-(4-methanesulfonylphenoxy)propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
29		1-methyl-1'-{2-[(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
30		1-methyl-1'-{2-[(2-methyl-1-oxo-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

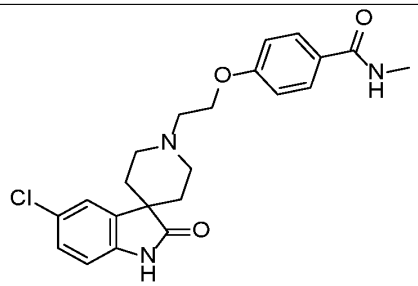
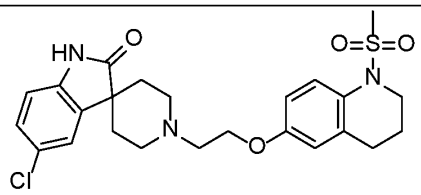
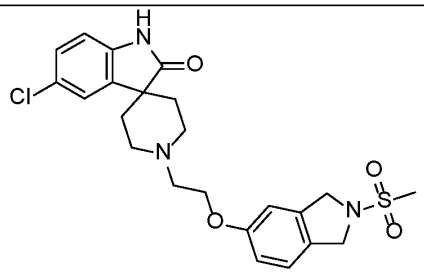
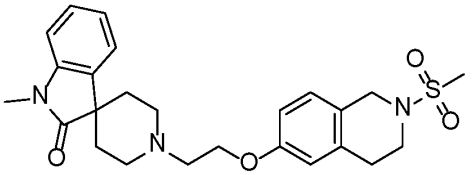
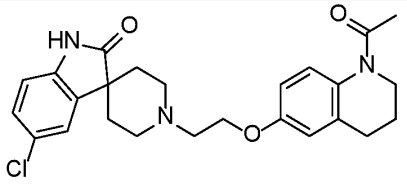
31		1-methyl-1'-{2-[4-(1-methyl-1H-pyrazol-4-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
32		5-(2-{1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,3-dihydro-1λ⁶-benzothiophene-1,1-dione
33		1-methyl-1'-{2-[(1-methyl-2-oxo-2,3-dihydro-1H-indol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
34		1-methyl-1'-[2-(quinoxalin-6-yloxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
35		1-methyl-1'-{2-[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

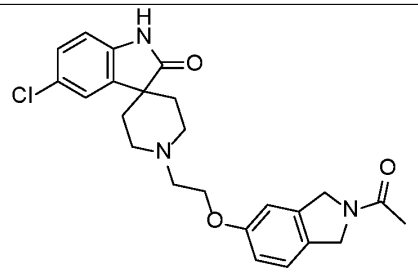
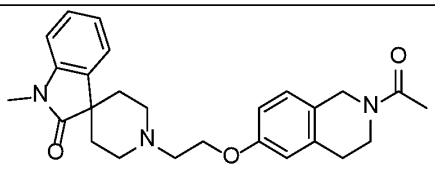
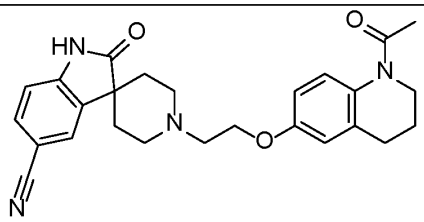
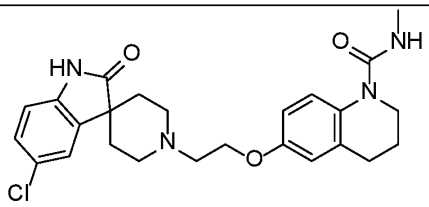
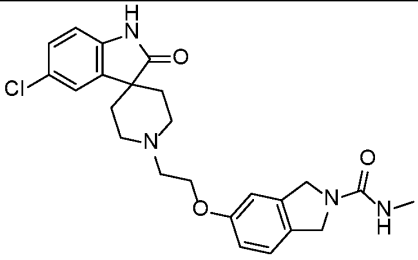
36		1'-{2-[(1-acetyl-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
37		1-methyl-1'-{2-[4-(2-oxopyrrolidin-1-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
38		5-chloro-1'-{2-[4-(1-methanesulfonylethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
39		5-chloro-1'-(2-{4-[(1S or 1R)-1-methanesulfonylethyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

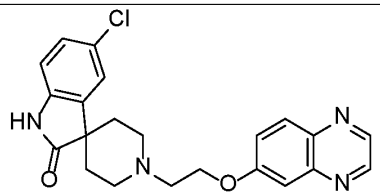
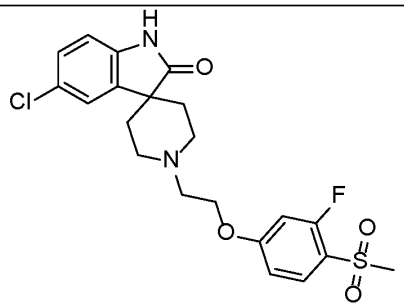
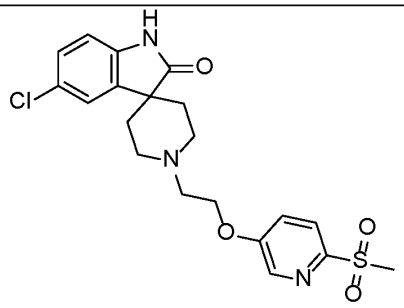
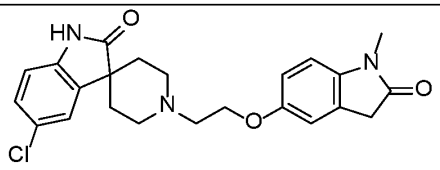
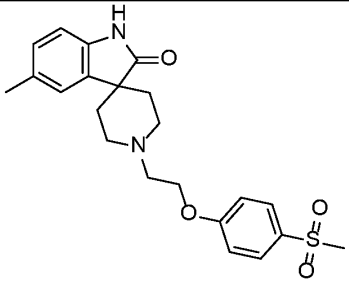
40		5-chloro-1'-(2-{4-[(1R or 1S)-1-methanesulfonylethyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
41		5-chloro-1'-{2-[4-(3-methanesulfonylpropanesulfonyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
42		1'-[2-(3,5-difluoro-4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
43		5-chloro-1'-{2-[4-(cyclopropanesulfonyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

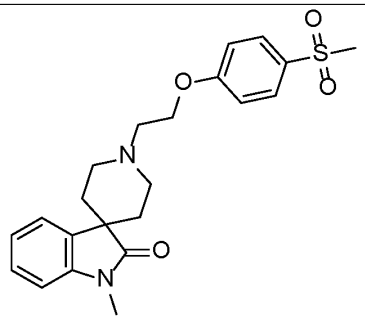
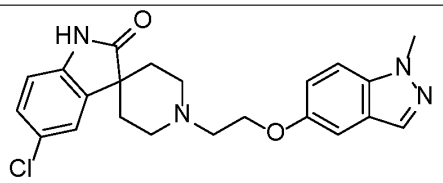
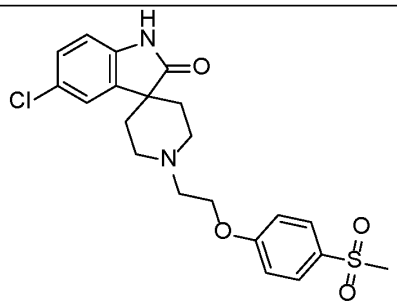
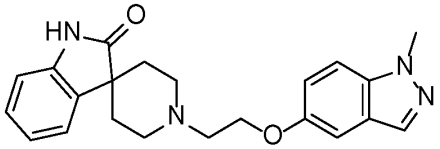
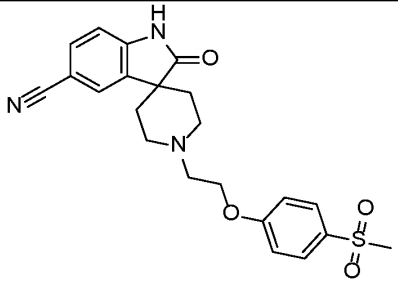
44		1'-[2-(4-difluoromethanesulfonylphenoxy) ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
45		4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzamide
46		4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzamide
47		5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)pyridine-2-carboxamide

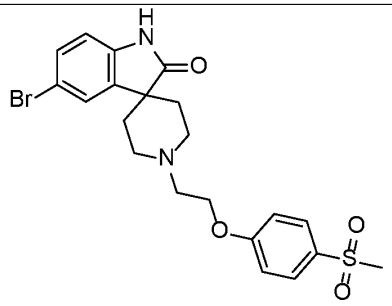
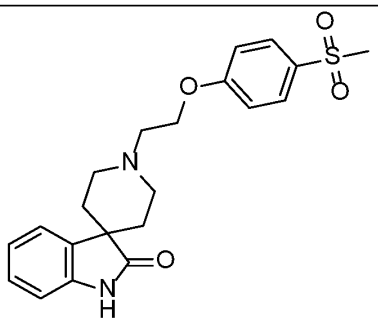
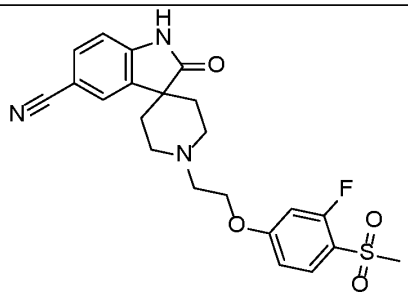
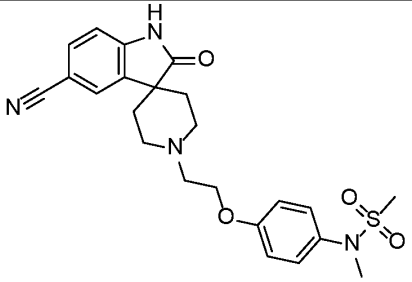
48		5-chloro-1'-[2-(2-fluoro-4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
49		4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-methylbenzamide
50		5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-methanesulfonylbenzonitrile
51		5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N,N-dimethylpyridine-2-carboxamide

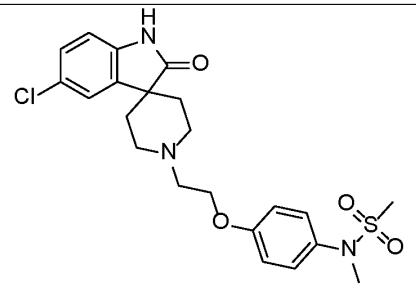
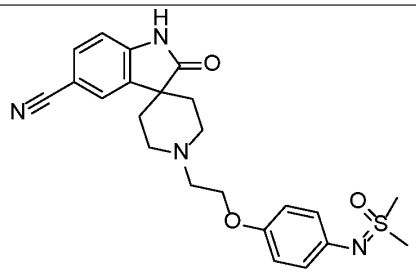
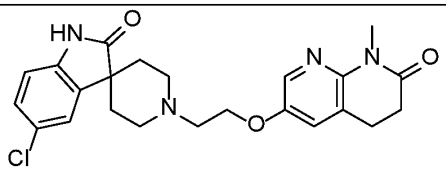
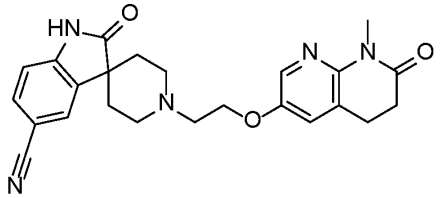
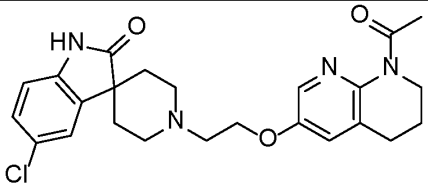
52		4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-methylbenzamide
53		5-chloro-1'-{2-[(1-methanesulfonyl-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
54		5-chloro-1'-{2-[(2-methanesulfonyl-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
55		1'-{2-[(2-methanesulfonyl-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy]ethyl}-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
56		1'-{2-[(1-acetyl-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

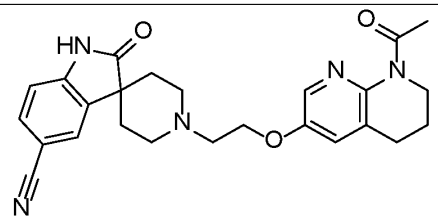
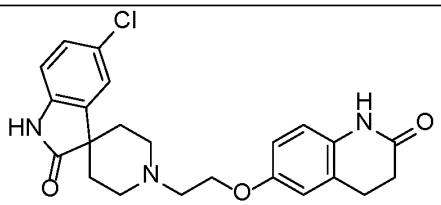
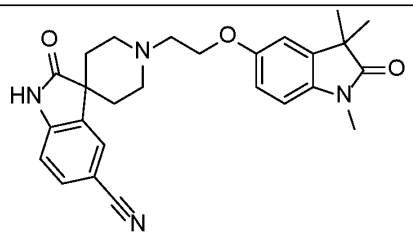
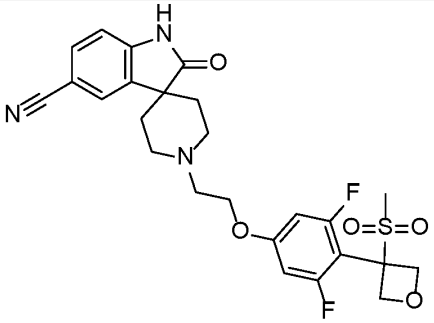
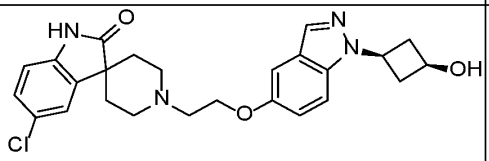
57		1'-{2-[(2-acetyl-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
58		1'-{2-[(2-acetyl-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy]ethyl}-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
59		1'-{2-[(1-acetyl-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
60		6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-methyl-1,2,3,4-tetrahydroquinoline-1-carboxamide
61		5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-methyl-2,3-dihydro-1H-isoindole-2-carboxamide

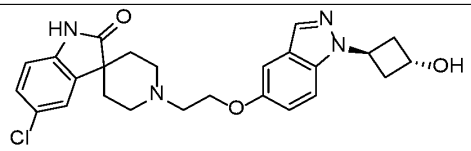
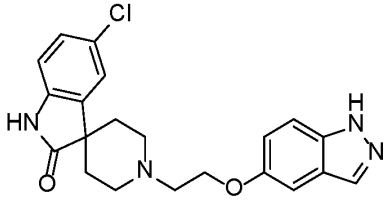
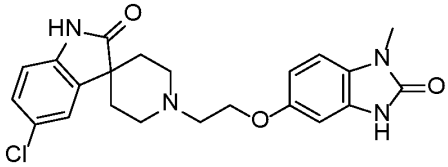
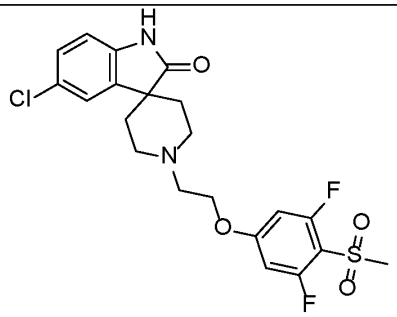
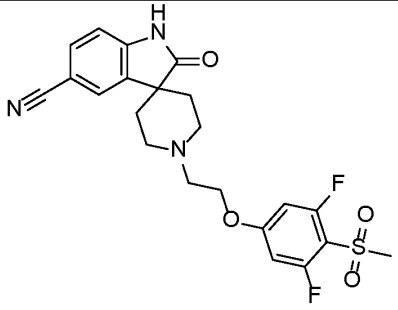
62		5-chloro-1'-[2-(quinoxalin-6-yloxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
63		5-chloro-1'-[2-(3-fluoro-4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
64		5-chloro-1'-{2-[(6-methanesulfonylpyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
65		5-chloro-1'-{2-[(1-methyl-2-oxo-2,3-dihydro-1H-indol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
66		1'-[2-(4-methanesulfonylphenoxy)ethyl]-5-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

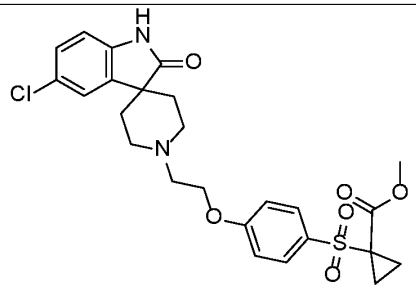
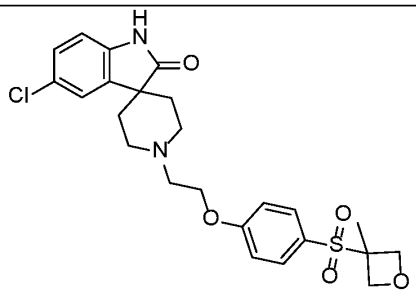
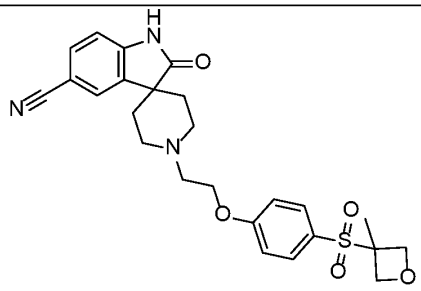
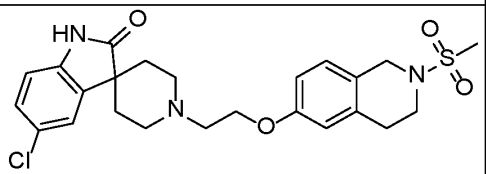
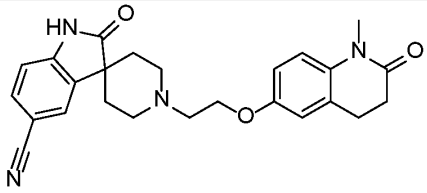
67		1'-[2-(4-methanesulfonylphenoxy)ethyl]-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
68		5-chloro-1'-{2-[(1-methyl-1H-indazol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
69		5-chloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
70		1'-{2-[(1-methyl-1H-indazol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
71		1'-[2-(4-methanesulfonylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile

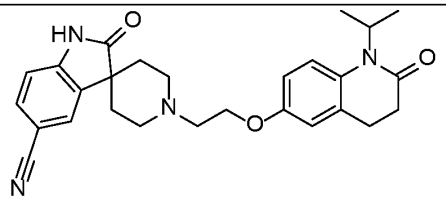
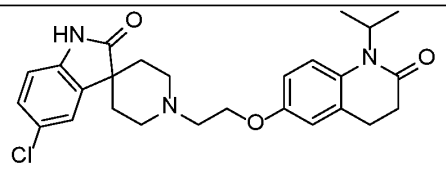
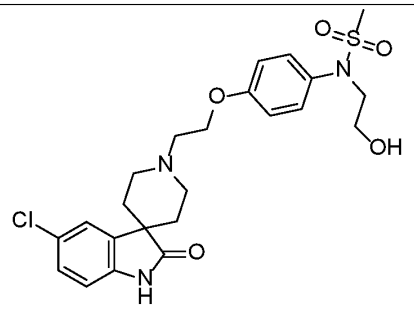
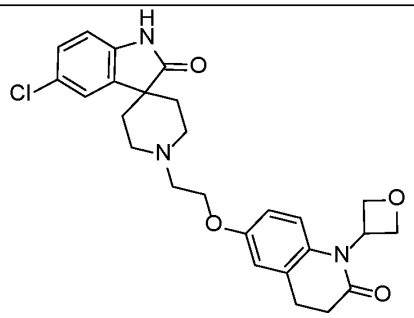
72		5-bromo-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-``one
73		1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
74		1'-[2-(3-fluoro-4-methanesulfonylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
75		N-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-N-methylmethanesulfonamide

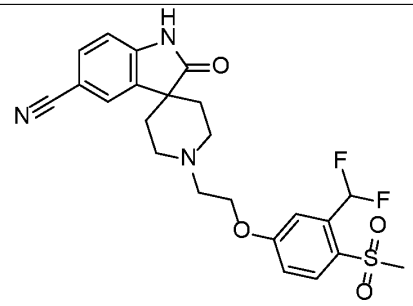
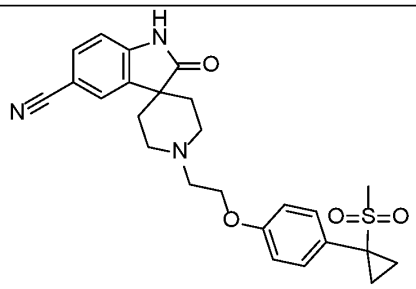
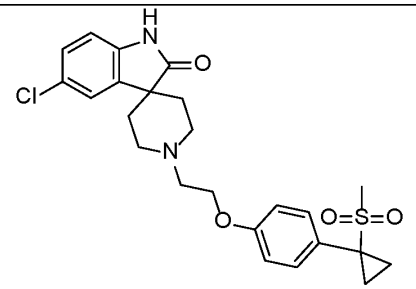
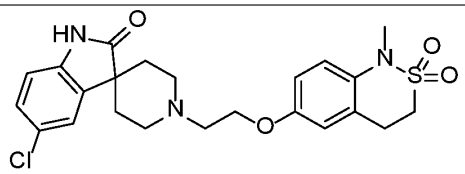
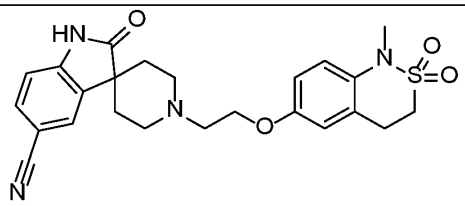
76		N-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-N-methylmethanesulfonamide
77		1'-[2-(4-{[dimethyl(oxo)-λ⁶-sulfanylidene]amino}phenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
78		5-chloro-1'-{2-[(8-methyl-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
79		1'-{2-[(8-methyl-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
80		1'-{2-[(8-acetyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

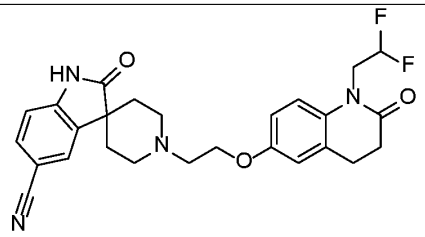
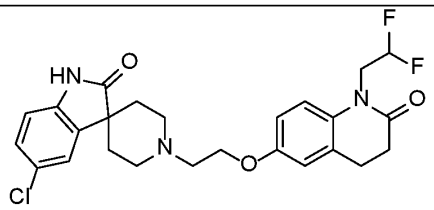
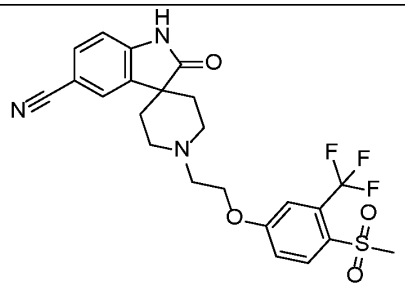
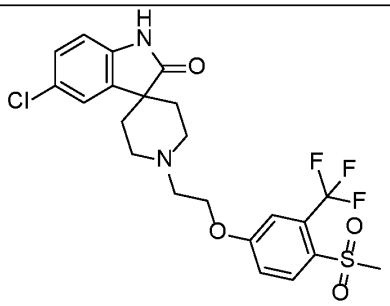
81		1'-{2-[(8-acetyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
82		5-chloro-1'-{2-[(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
83		2-oxo-1'-{2-[(1,3,3-trimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
84		1'-{2-[3,5-difluoro-4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
85		5-chloro-1'-[2-({1-[(cis)-3-hydroxycyclobutyl]-1H-indazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

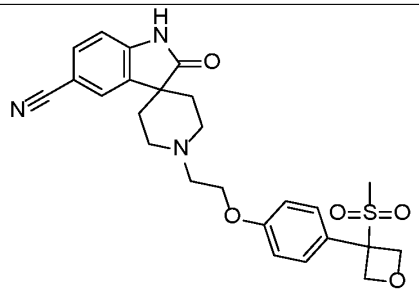
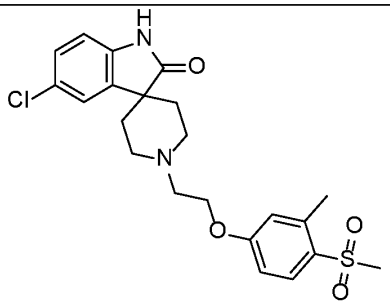
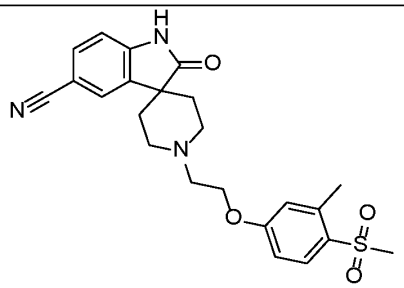
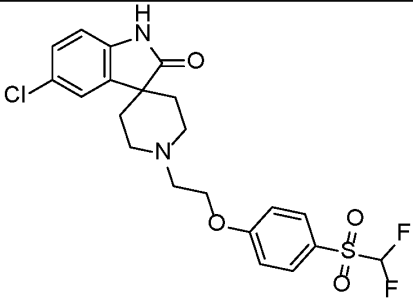
86		5-chloro-1'-[2-({1-[(trans)-3-hydroxycyclobutyl]-1H-indazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
87		5-chloro-1'-[2-(1H-indazol-5-yloxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
88		5-chloro-1'-{2-[(1-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
89		5-chloro-1'-[2-(3,5-difluoro-4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
90		1'-[2-(3,5-difluoro-4-methanesulfonylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile

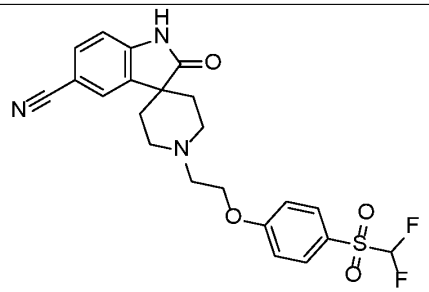
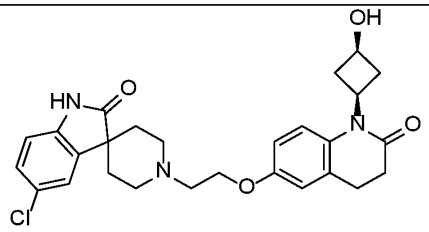
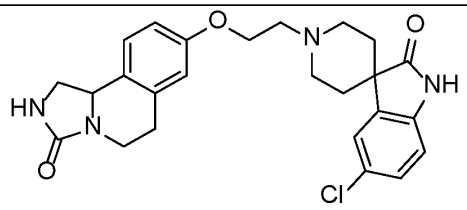
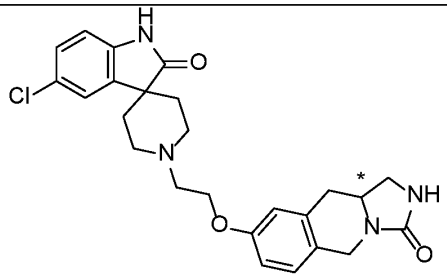
91		methyl 1-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzenesulfonyl]cyclopropane-1-carboxylate
92		5-chloro-1'-(2-{4-[(3-methyloxetan-3-yl)sulfonyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
93		1'-(2-{4-[(3-methyloxetan-3-yl)sulfonyl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
94		5-chloro-1'-{2-[(2-methanesulfonyl-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
95		1'-{2-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-2-oxo-1,2-

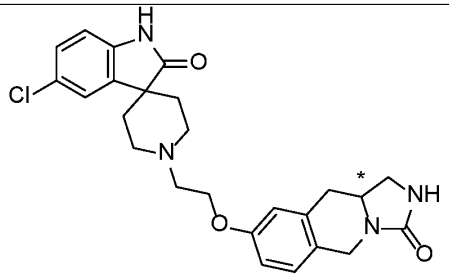
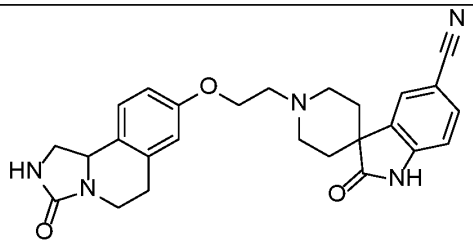
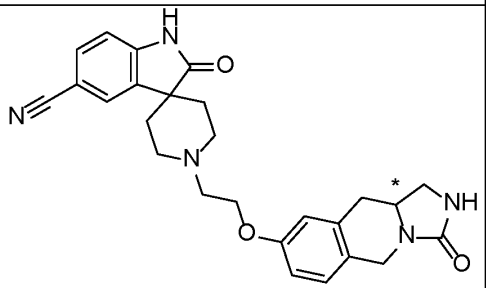
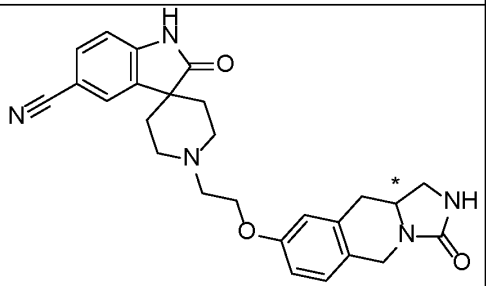
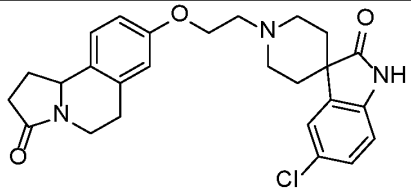
		dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
96		2-oxo-1'-(2-{[2-oxo-1-(propan-2-yl)-1,2,3,4-tetrahydroquinolin-6-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
97		5-chloro-1'-(2-{[2-oxo-1-(propan-2-yl)-1,2,3,4-tetrahydroquinolin-6-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
98		N-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-N-(2-hydroxyethyl)methanesulfonamide
99		5-chloro-1'-(2-{[1-(oxetan-3-yl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

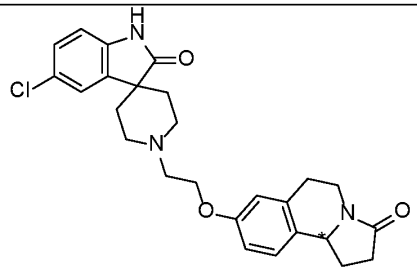
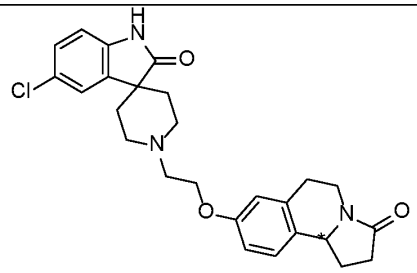
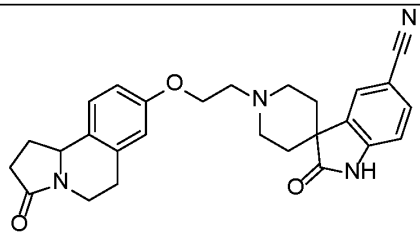
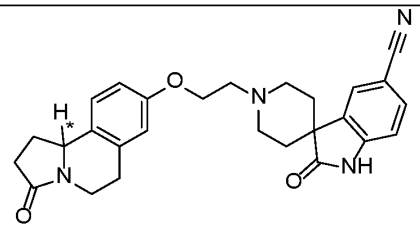
100		1'-{2-[3-(difluoromethyl)-4-methanesulfonylphenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
101		1'-{2-[4-(1-methanesulfonylcyclopropyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
102		5-chloro-1'-{2-[4-(1-methanesulfonylcyclopropyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
103		6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-1-methyl-3,4-dihydro-1H-2λ⁶,1-benzothiazine-2,2-dione
104		1'-{2-[(1-methyl-2,2-dioxo-3,4-dihydro-1H-2λ⁶,1-benzothiazin-6-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile

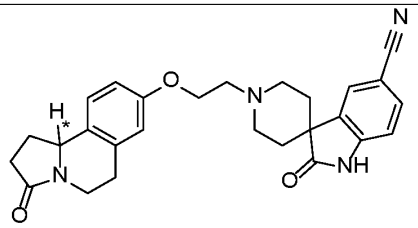
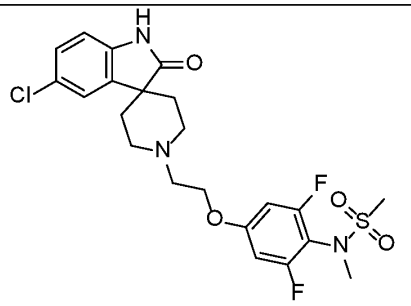
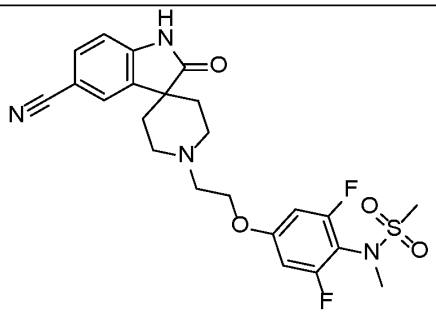
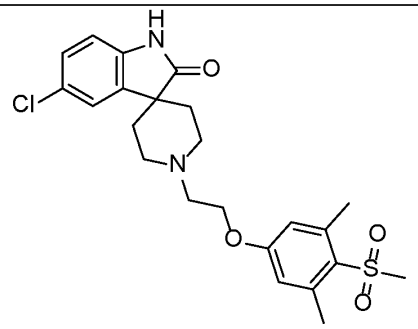
105		1'-(2-{[1-(2,2-difluoroethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
106		5-chloro-1'-(2-{[1-(2,2-difluoroethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
107		1'-{2-[4-methanesulfonyl-3-(trifluoromethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
108		5-chloro-1'-{2-[4-methanesulfonyl-3-(trifluoromethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

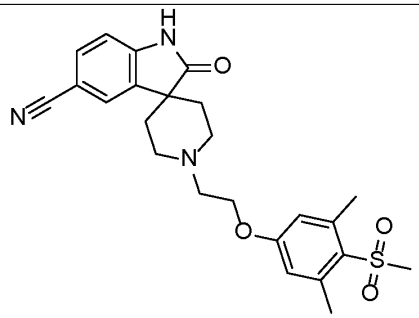
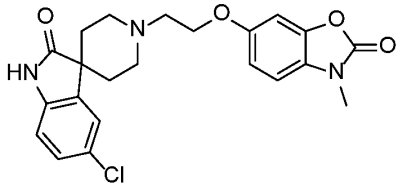
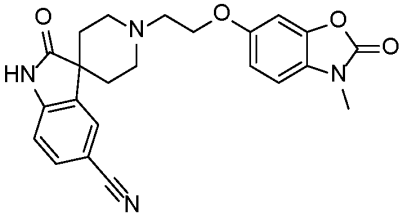
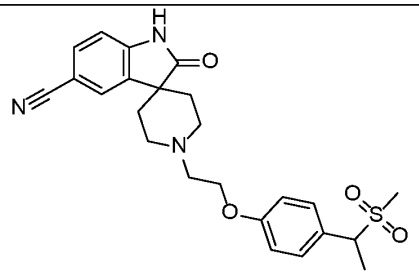
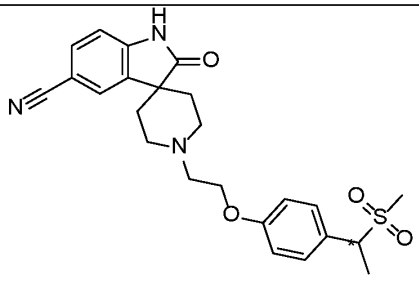
109		1'-{2-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
110		5-chloro-1'-[2-(4-methanesulfonyl-3-methylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
111		1'-[2-(4-methanesulfonyl-3-methylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
112		5-chloro-1'-[2-(4-difluoromethanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

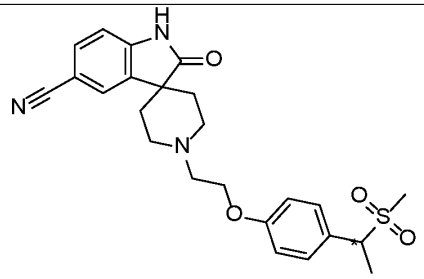
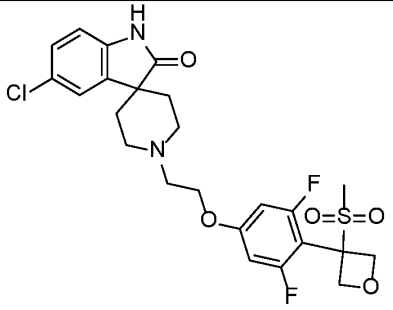
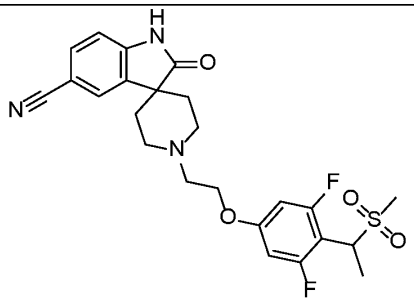
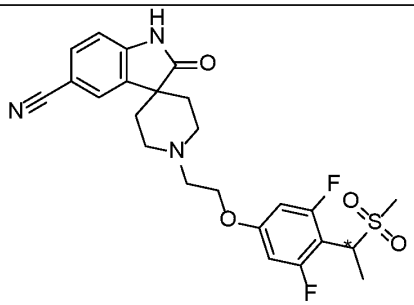
113		1'-[2-(4-difluoromethanesulfonylphenoxy) ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
114		5-chloro-1'-[2-({2-oxo-1-[(cis)-3-hydroxycyclobutyl]-1,2,3,4-tetrahydroquinolin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
115		5-chloro-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
116		(S) or (R)-5-chloro-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

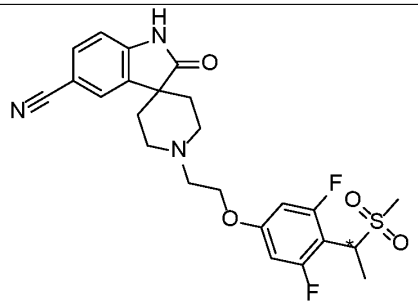
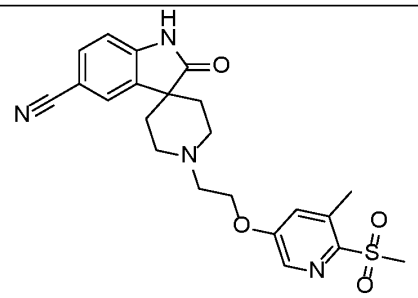
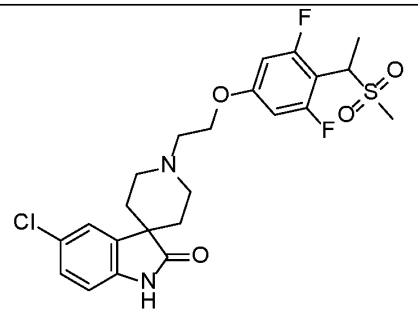
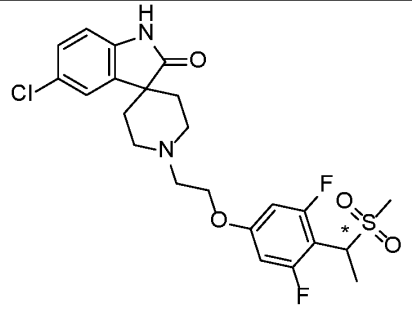
117		(R) or (S)-5-chloro-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
118		2-oxo-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
119		(S) or (R)-2-oxo-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
120		(R) or (S)-2-oxo-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
121		5-chloro-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinolin-8-yl}oxy)ethyl]-1,2-

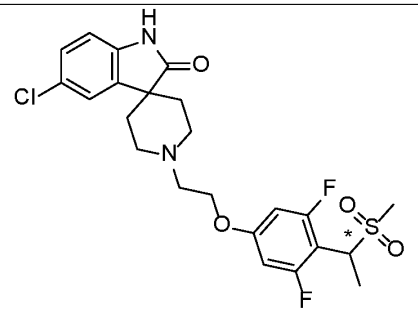
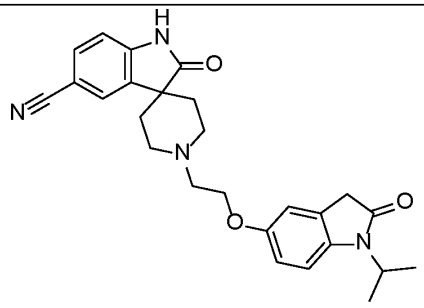
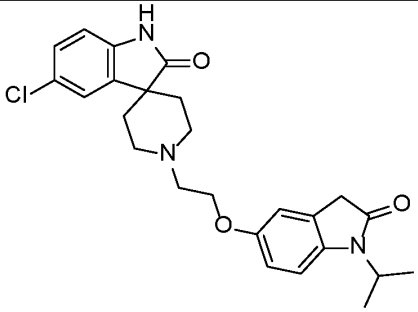
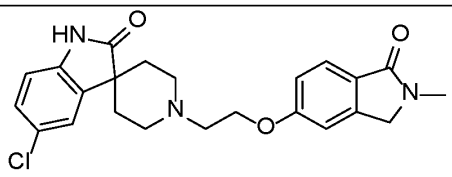
		dihydrospiro[indole-3,4'-piperidin]-2-one
122		(S) or (R)-5-chloro-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
123		(R) or (S)-5-chloro-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
124		2-oxo-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
125		(S) or (R)-2-oxo-1'-(2-((3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-8-yl)oxy)ethyl)spiro[indoline-3,4'-piperidine]-5-carbonitrile

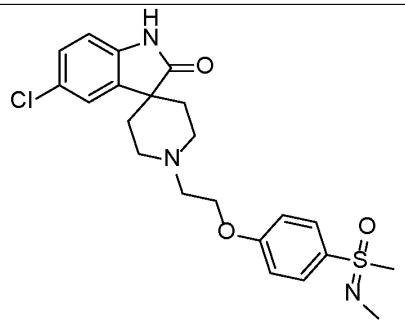
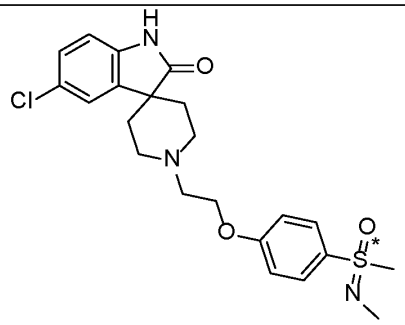
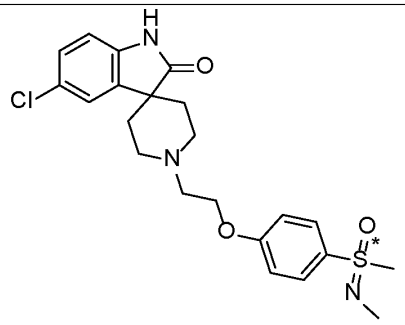
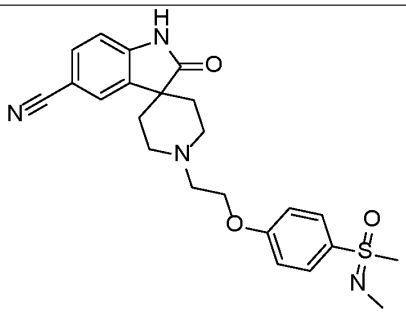
126		(R) or (S)-2-oxo-1'-(2-((3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-8-yl)oxy)ethyl)spiro[indoline-3,4'-piperidine]-5-carbonitrile
127		N-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,6-difluorophenyl]-N-methylmethanesulfonamide
128		N-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,6-difluorophenyl]-N-methylmethanesulfonamide
129		5-chloro-1'-[2-(4-methanesulfonyl-3,5-dimethylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

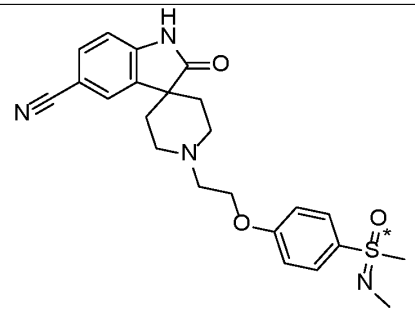
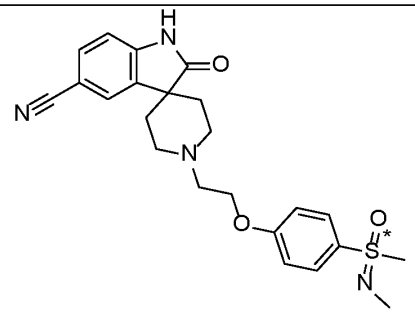
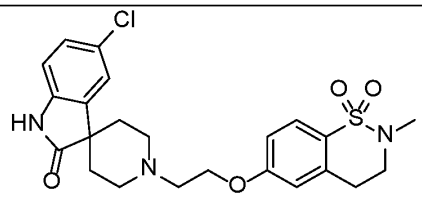
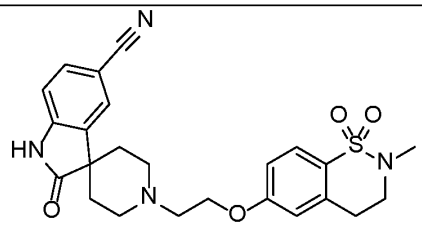
130		1'-[2-(4-methanesulfonyl-3,5-dimethylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
131		5-chloro-1'-{2-[(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
132		1'-{2-[(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
133		1'-{2-[4-(1-methanesulfonylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
134		(S) or (R)-1'-{2-[4-(1-methanesulfonylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile

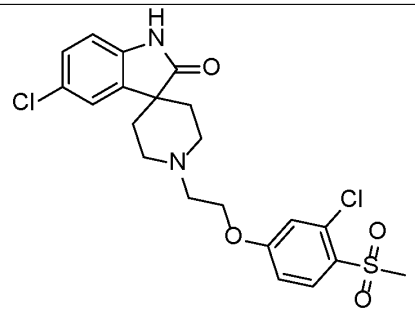
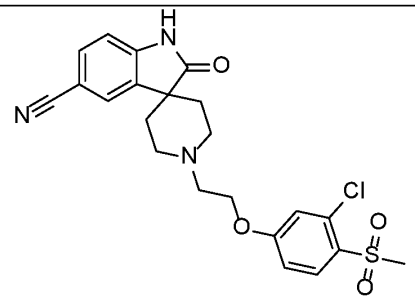
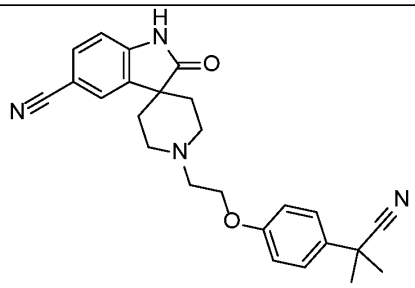
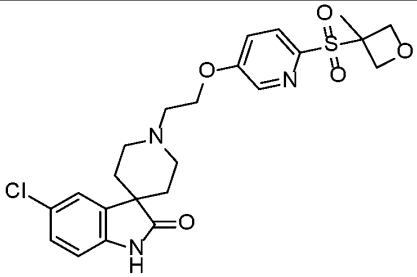
135		(R) or (S)-1'-{2-[4-(1-methanesulfonylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
136		5-chloro-1'-{2-[3,5-difluoro-4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
137		1'-{2-[3,5-difluoro-4-(1-methanesulfonylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
138		(S) or (R)-1'-{2-[3,5-difluoro-4-(1-methanesulfonylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile

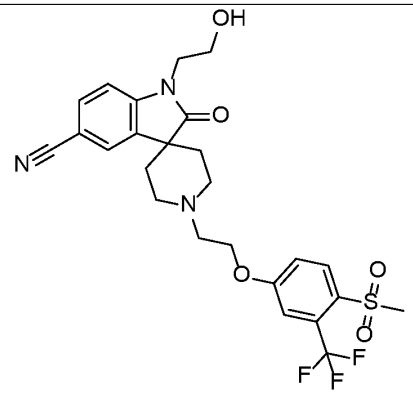
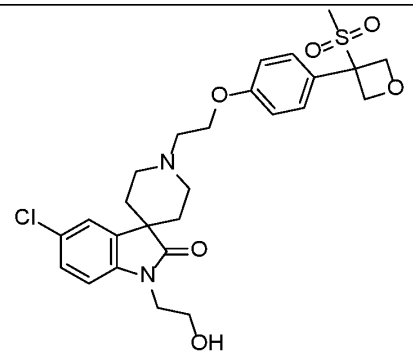
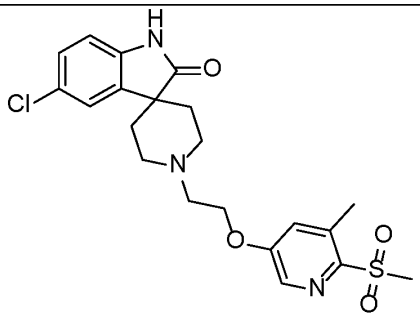
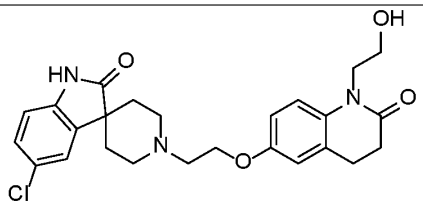
139		(R) or (S)-1'-{2-[3,5-difluoro-4-(1-methanesulfonylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
140		1'-{2-[(6-methanesulfonyl-5-methylpyridin-3-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
141		5-chloro-1'-{2-[3,5-difluoro-4-(1-methanesulfonylethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
142		(S) or (R)-5-chloro-1'-{2-[3,5-difluoro-4-(1-methanesulfonylethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

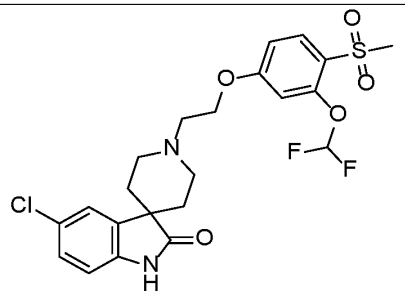
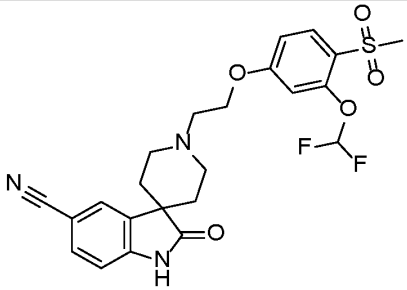
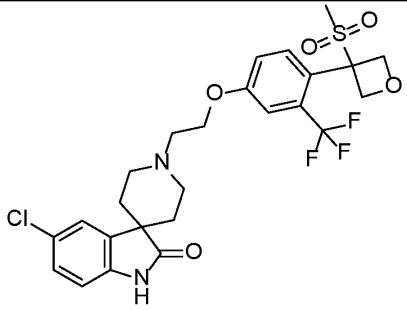
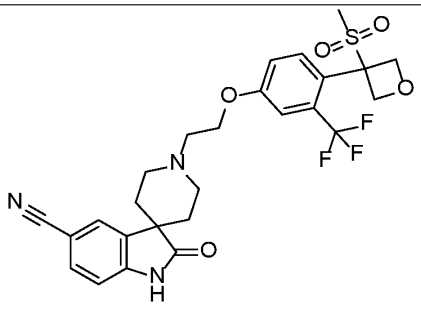
143		(R) or (S)-5-chloro-1'-{2-[3,5-difluoro-4-(1-methanesulfonylethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
144		2-oxo-1'-(2-{[2-oxo-1-(propan-2-yl)-2,3-dihydro-1H-indol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
145		5-chloro-1'-(2-{[2-oxo-1-(propan-2-yl)-2,3-dihydro-1H-indol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
146		5-chloro-1'-{2-[(2-methyl-1-oxo-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

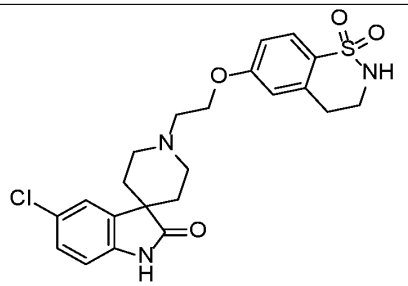
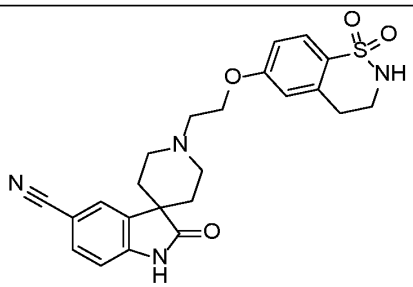
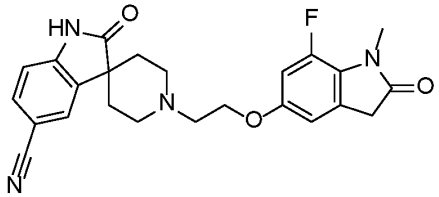
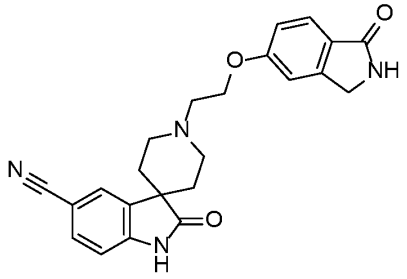
147		5-chloro-1'-(2-{4-[methyl(methylimino)oxo-λ⁶-sulfanyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
148		(S) or (R)-5-chloro-1'-(2-{4-[methyl(methylimino)oxo-λ⁶-sulfanyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
149		(R) or (S)-5-chloro-1'-(2-{4-[methyl(methylimino)oxo-λ⁶-sulfanyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
150		1'-(2-{4-[methyl(methylimino)oxo-λ⁶-sulfanyl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile

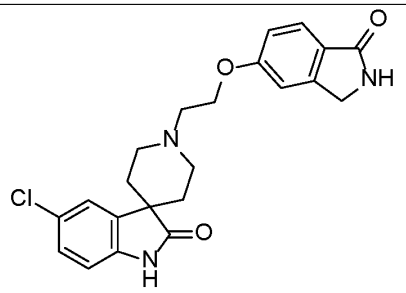
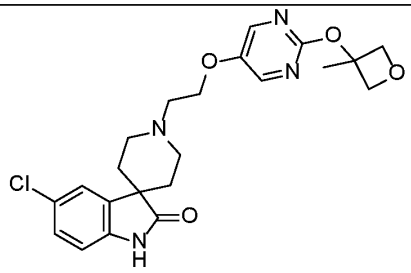
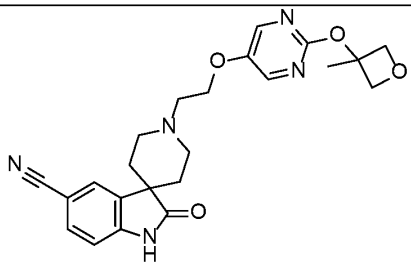
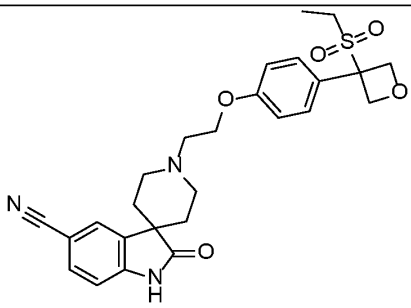
151		(S) or (R)-1'-(2-{4-[methyl(methylimino)oxo-λ⁶-sulfanyl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
152		(R) or (S)-1'-(2-{4-[methyl(methylimino)oxo-λ⁶-sulfanyl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
153		6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-methyl-3,4-dihydro-2H-1λ⁶,2-benzothiazine-1,1-dione
154		1'-{2-[(2-methyl-1,1-dioxo-3,4-dihydro-2H-1λ⁶,2-benzothiazin-6-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile

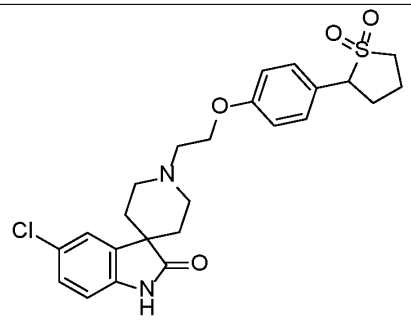
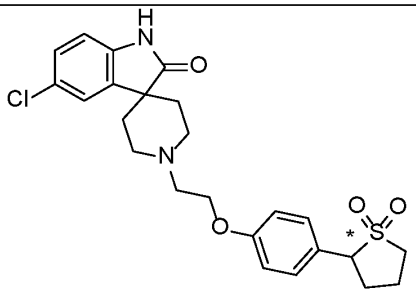
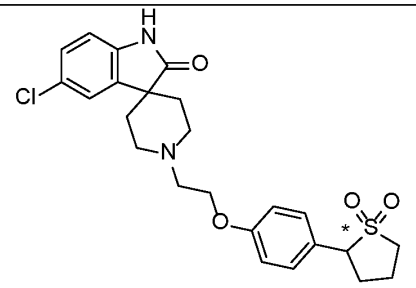
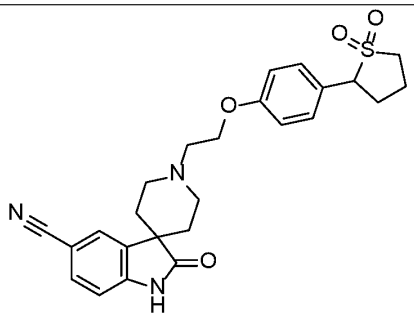
155		5-chloro-1'-[2-(3-chloro-4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
156		1'-[2-(3-chloro-4-methanesulfonylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
157		1'-{2-[4-(1-cyano-1-methylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
158		5-chloro-1'-[2-({6-[(3-methyloxetan-3-yl)sulfonyl]pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

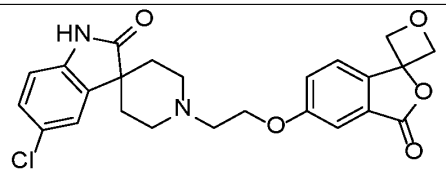
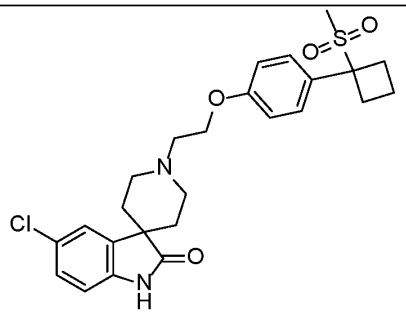
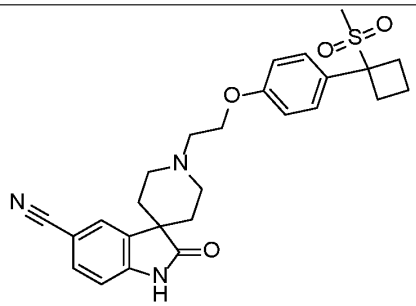
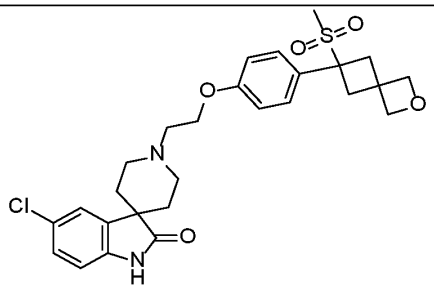
159		1-(2-hydroxyethyl)-1'-{2-[4-methanesulfonyl-3-(trifluoromethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
160		5-chloro-1-(2-hydroxyethyl)-1'-{2-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
161		5-chloro-1'-{2-[(6-methanesulfonyl-5-methylpyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
162		5-chloro-1'-(2-{[1-(2-hydroxyethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

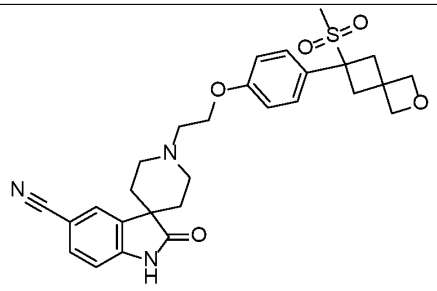
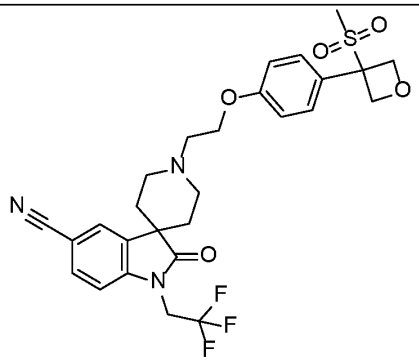
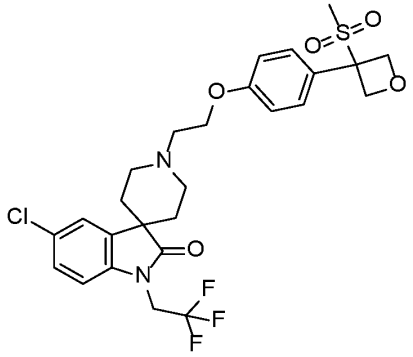
163		5-chloro-1'-{2-[3-(difluoromethoxy)-4-methanesulfonylphenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
164		1'-{2-[3-(difluoromethoxy)-4-methanesulfonylphenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
165		5-chloro-1'-{2-[4-(3-methanesulfonyloxetan-3-yl)-3-(trifluoromethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
166		1'-{2-[4-(3-methanesulfonyloxetan-3-yl)-3-(trifluoromethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile

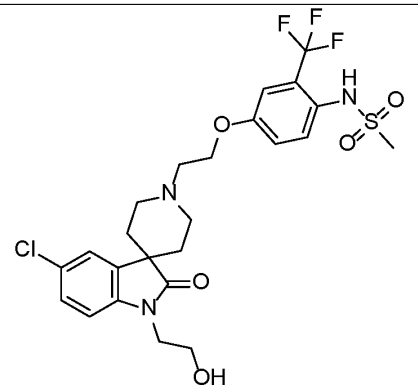
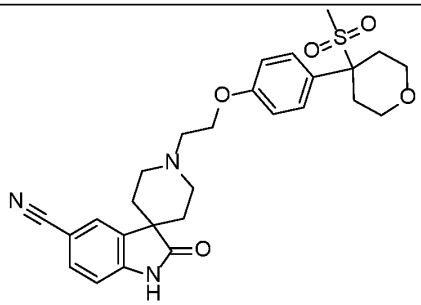
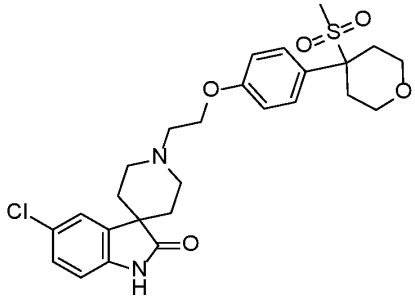
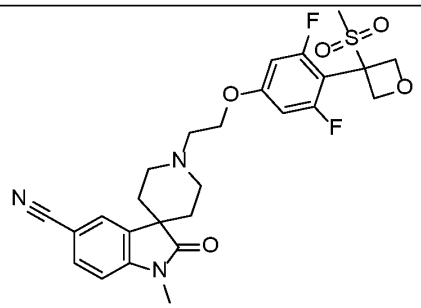
167		6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-3,4-dihydro-2H-1λ⁶,2-benzothiazine-1,1-dione
168		1'-{2-[(1,1-dioxo-3,4-dihydro-2H-1λ⁶,2-benzothiazin-6-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
169		1'-{2-[(7-fluoro-1-methyl-2-oxo-2,3-dihydro-1H-indol-5-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
170		2-oxo-1'-{2-[(1-oxo-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile

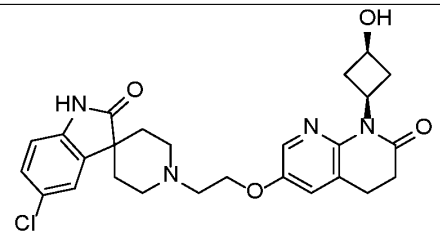
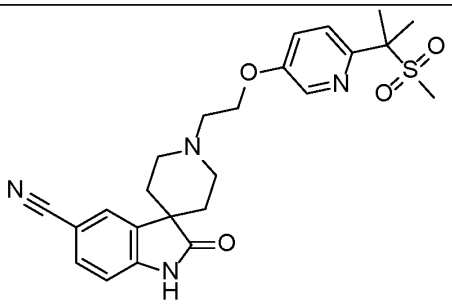
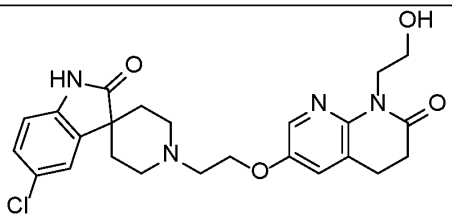
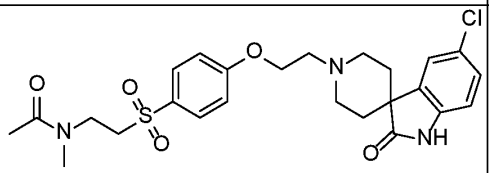
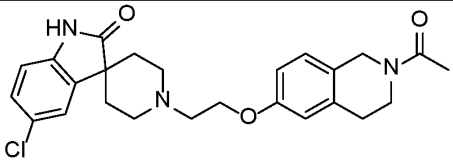
171		5-chloro-1'-{2-[(1-oxo-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
172		5-chloro-1'-[2-({2-[(3-methyloxetan-3-yl)oxy]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
173		1'-[2-({2-[(3-methyloxetan-3-yl)oxy]pyrimidin-5-yl}oxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
174		1'-(2-{4-[3-(ethanesulfonyl)oxetan-3-yl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile

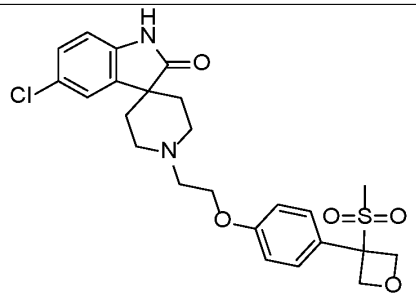
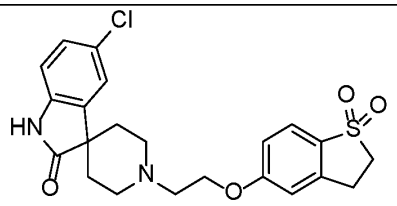
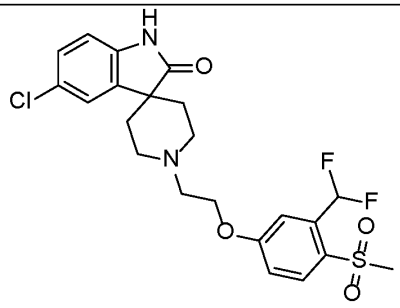
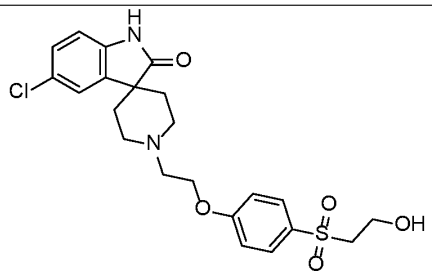
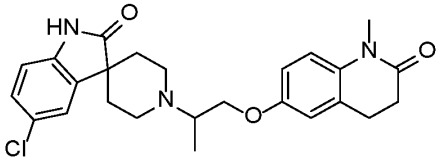
175		2-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-1λ⁶-thiolane-1,1-dione
176		(S) or (R)-2-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-1λ⁶-thiolane-1,1-dione
177		(R) or (S)-2-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-1λ⁶-thiolane-1,1-dione
178		1'-{2-[4-(1,1-dioxo-1λ⁶-thiolan-2-yl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile

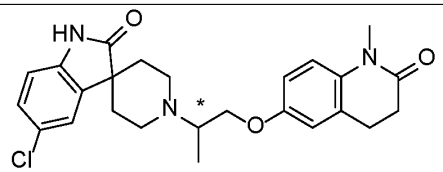
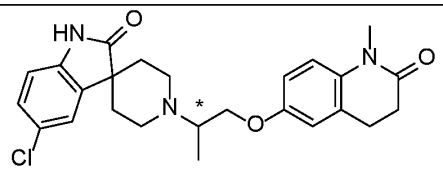
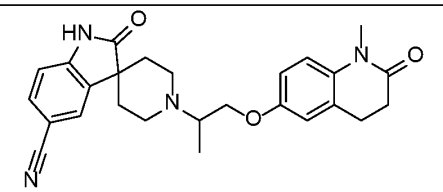
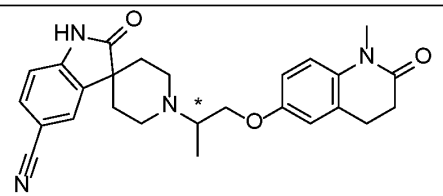
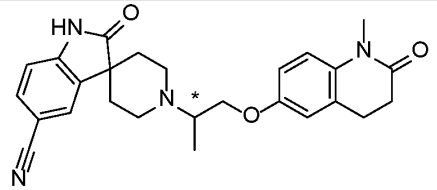
179		5-chloro-1'-(2-{3-oxo-3H-spiro[2-benzofuran-1,3'-oxetan]-5-yloxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
180		5-chloro-1'-{2-[4-(1-methanesulfonylcyclobutyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
181		1'-{2-[4-(1-methanesulfonylcyclobutyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
182		5-chloro-1'-[2-(4-{6-methanesulfonyl-2-oxaspiro[3.3]heptan-6-yl}phenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

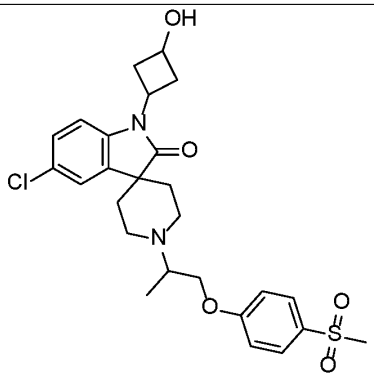
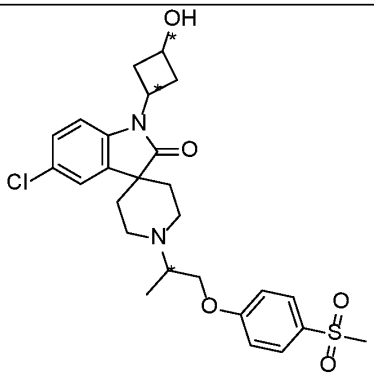
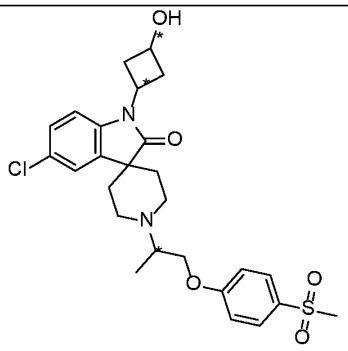
183		1'-[2-(4-{6-methanesulfonyl-2-oxaspiro[3.3]heptan-6-yl}phenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
184		1'-{2-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-2-oxo-1-(2,2,2-trifluoroethyl)-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
185		5-chloro-1'-{2-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-1-(2,2,2-trifluoroethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

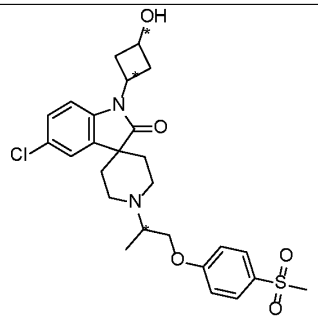
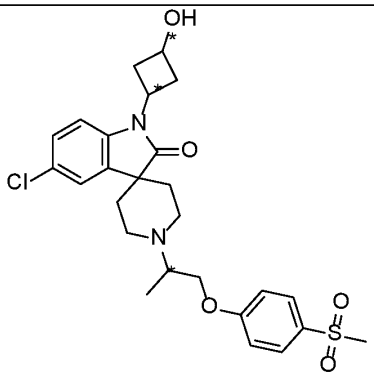
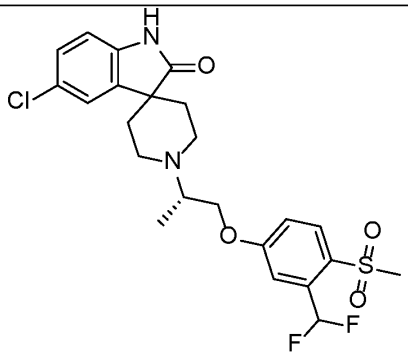
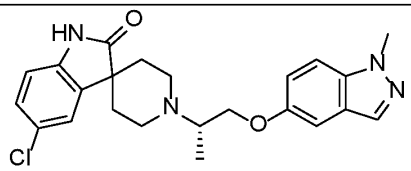
186		N-(4-{2-[5-chloro-1-(2-hydroxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl]ethoxy}-2-(trifluoromethyl)phenyl)methanesulfonamide
187		1'-{2-[4-(4-methanesulfonyloxan-4-yl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
188		5-chloro-1'-{2-[4-(4-methanesulfonyloxan-4-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
189		1'-{2-[3,5-difluoro-4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile

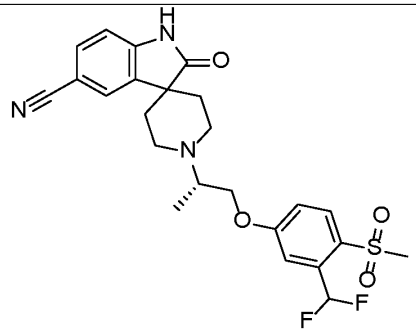
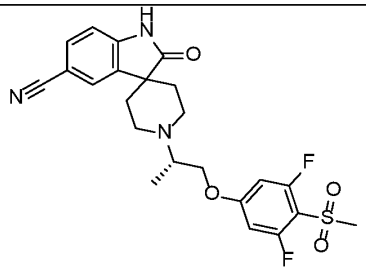
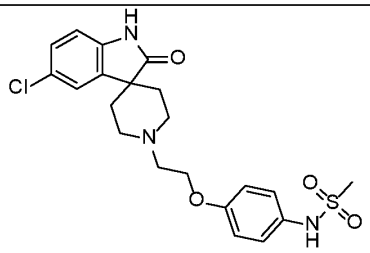
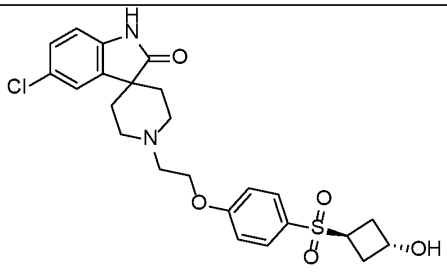
190		5-chloro-1'-[2-({7-oxo-8-[(cis)-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
191		1'-(2-{[6-(2-methanesulfonylpropan-2-yl)pyridin-3-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
192		5-chloro-1'-(2-{[8-(2-hydroxyethyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
193		N-{2-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzenesulfonyl]ethyl}-N-methylacetamide
194		1'-{2-[(2-acetyl-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy]ethyl}-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

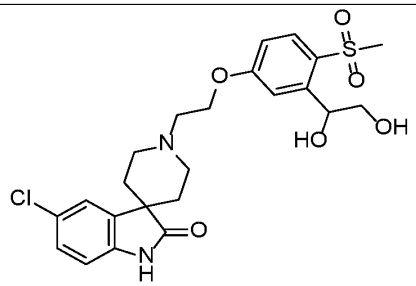
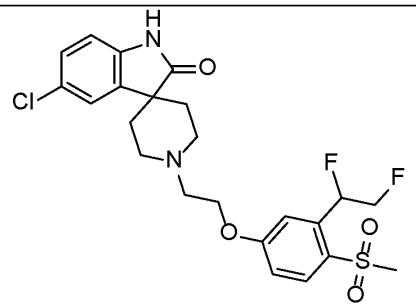
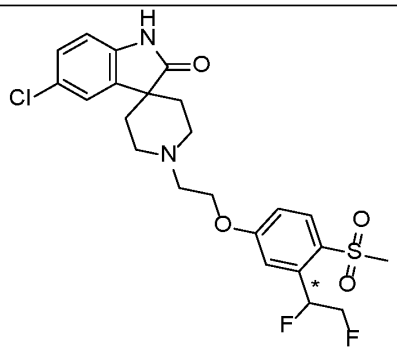
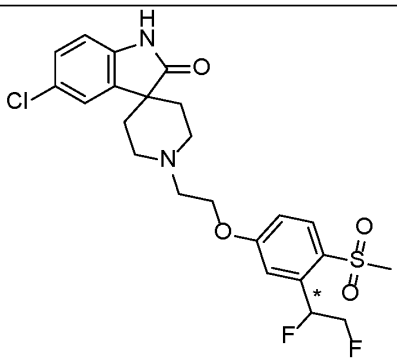
195		5-chloro-1'-{2-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
196		5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,3-dihydro-1λ⁶-benzothiophene-1,1-dione
197		5-chloro-1'-{2-[3-(difluoromethyl)-4-methanesulfonylphenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
198		5-chloro-1'-{2-[4-(2-hydroxyethanesulfonyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
199		5-chloro-1'-{1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

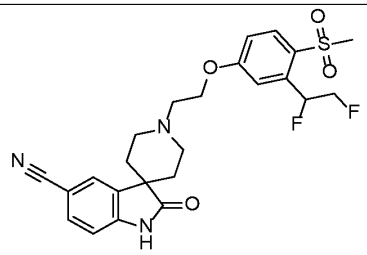
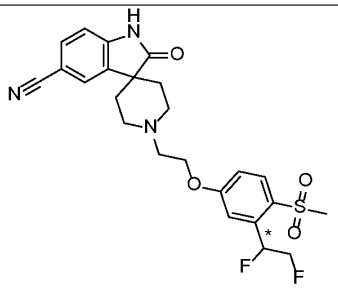
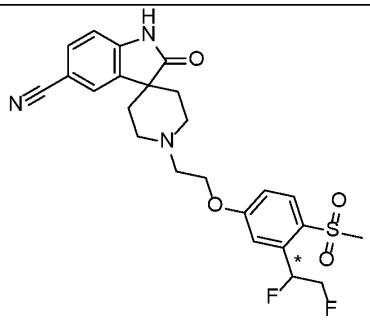
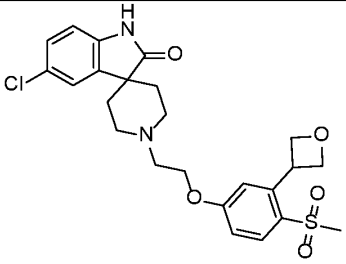
200		chloro-1'-[(2S) or (2R)-1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
201		chloro-1'-[(2R) or (2S)-1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
202		1'-{1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
203		(S) or (R)-1'-{1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
204		(R) or (S)-1'-{1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile

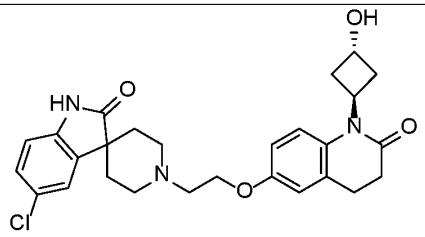
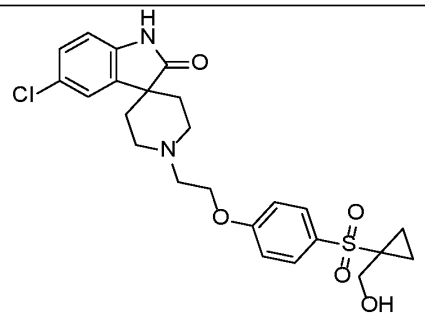
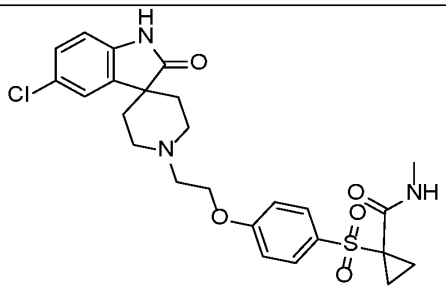
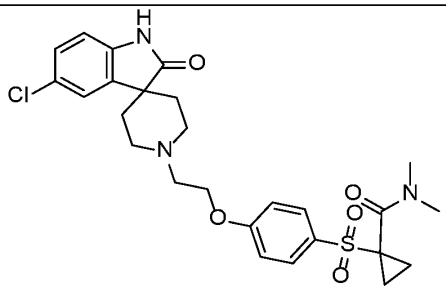
205		5-chloro-1'-[1-(4-methanesulfonylphenoxy)propan-2-yl]-1-[3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
206		5-chloro-1'-[(2*S*) or (2*R*) -1-(4-methanesulfonylphenoxy)propan-2-yl]-1-[(*cis*) or (*trans*)-3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
207		5-chloro-1'-[(2*S*) or (2*R*) -1-(4-methanesulfonylphenoxy)propan-2-yl]-1-[(*trans*) or (*cis*)-3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

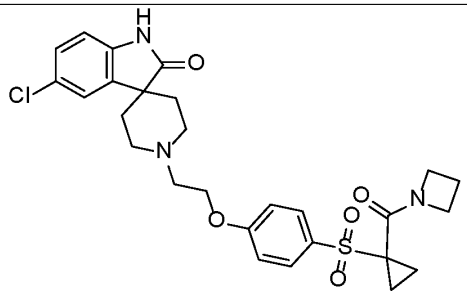
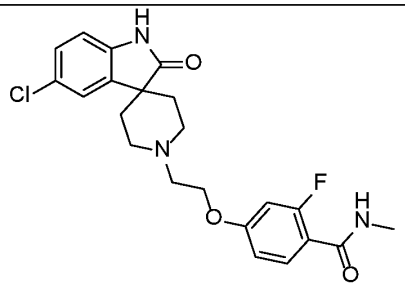
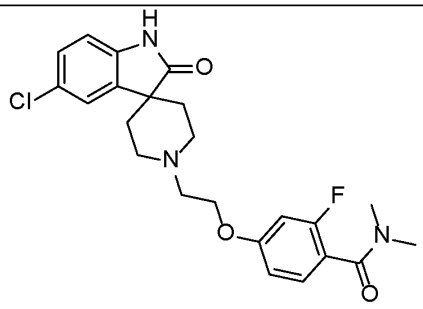
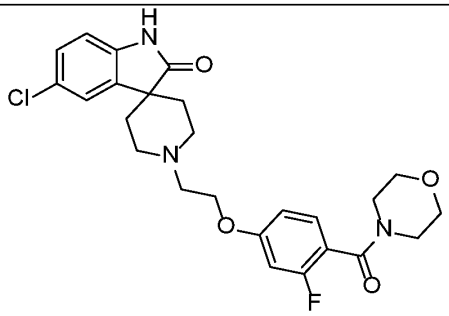
208		5-chloro-1'-[(2*R*) or (2*S*) -1-(4-methanesulfonylphenoxy)propan-2-yl]-1-[(*cis*) or (*trans*)-3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
209		5-chloro-1'-[(2*R*) or (2*S*) -1-(4-methanesulfonylphenoxy)propan-2-yl]-1-[(*trans*) or (*cis*)-3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
210		5-chloro-1'-[(2S)-1-[3-(difluoromethyl)-4-methanesulfonylphenoxy]propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
211		5-chloro-1'-[(2S)-1-[(1-methyl-1H-indazol-5-yl)oxy]propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

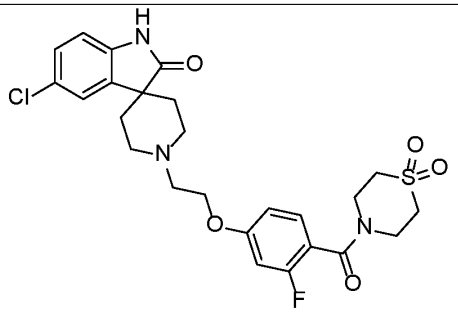
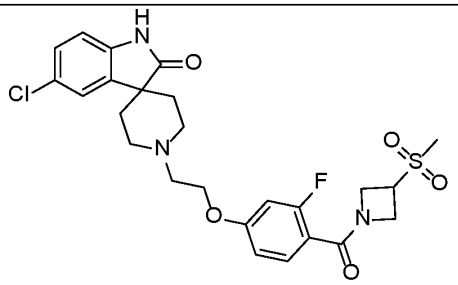
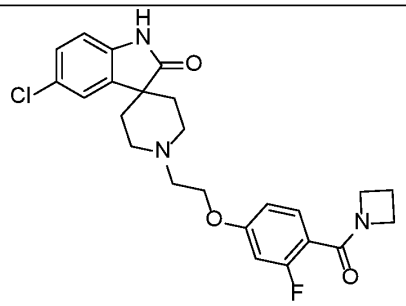
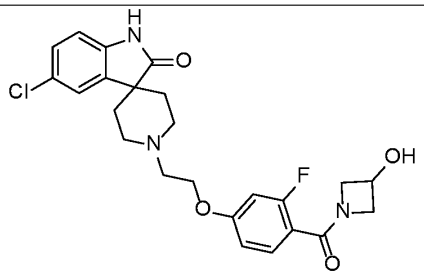
212		1'-[(2S)-1-[3-(difluoromethyl)-4-methanesulfonylphenoxy]propan-2-yl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
213		1'-[(2S)-1-(3,5-difluoro-4-methanesulfonylphenoxy)propan-2-yl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
214		N-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]methanesulfonamide
215		5-chloro-1'-[2-(4-{[(trans)-3-hydroxycyclobutyl]sulfonyl}phenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

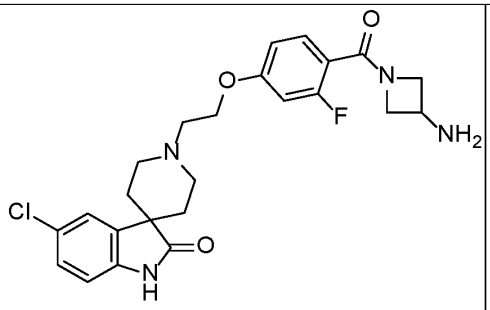
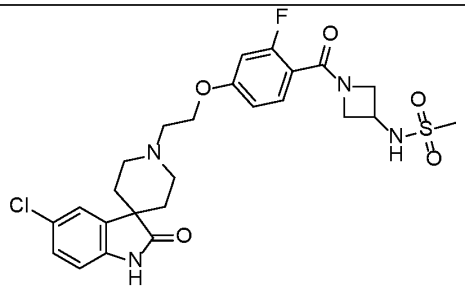
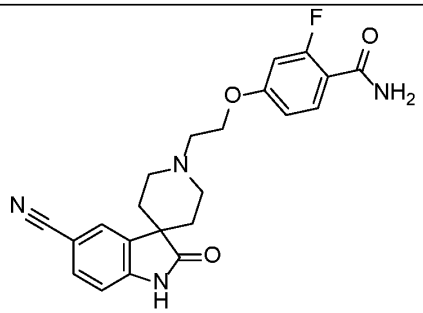
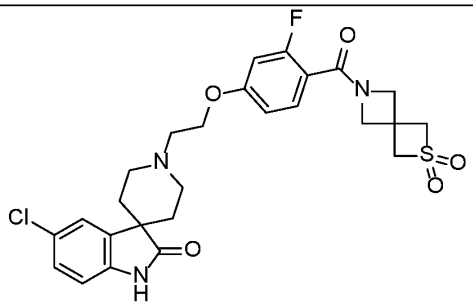
216		5-chloro-1'-{2-[3-(1,2-dihydroxyethyl)-4-methanesulfonylphenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
217		5-chloro-1'-{2-[3-(1,2-difluoroethyl)-4-methanesulfonylphenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
218		5-chloro-1'-(2-{3-[(1S or 1R)-1,2-difluoroethyl]-4-methanesulfonylphenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
219		5-chloro-1'-(2-{3-[(1R or 1S)-1,2-difluoroethyl]-4-methanesulfonylphenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

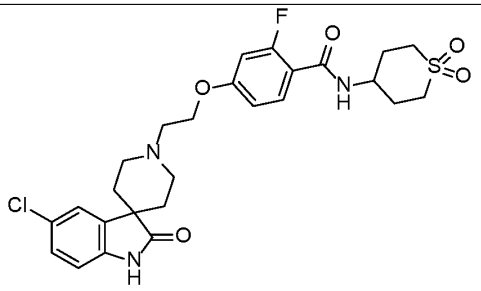
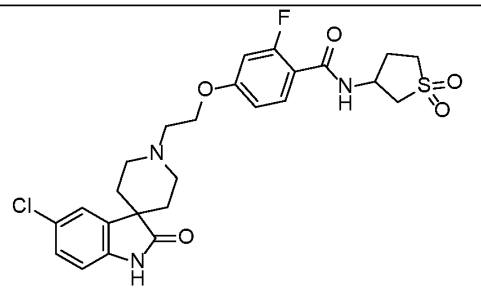
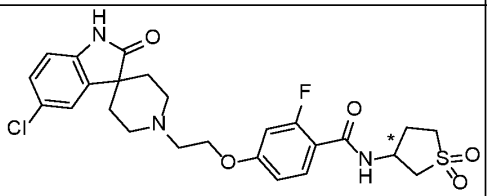
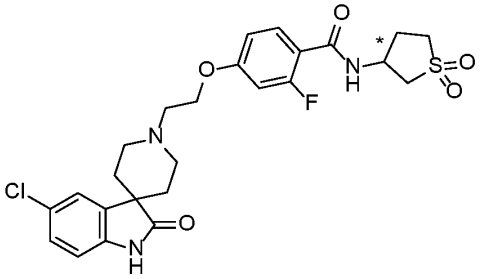
220		1'-{2-[3-(1,2-difluoroethyl)-4-methanesulfonylphenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
221		1'-(2-{3-[(1S or 1R)-1,2-difluoroethyl]-4-methanesulfonylphenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
222		1'-(2-{3-[(1R or 1S)-1,2-difluoroethyl]-4-methanesulfonylphenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
223		5-chloro-1'-{2-[4-methanesulfonyl-3-(oxetan-3-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
224		5-chloro-1'-[2-({2-oxo-1-[(trans)-3-hydroxycyclobutyl]-1,2,3,4-tetrahydroquinolin-6-yl}oxy)ethyl]-1,2-

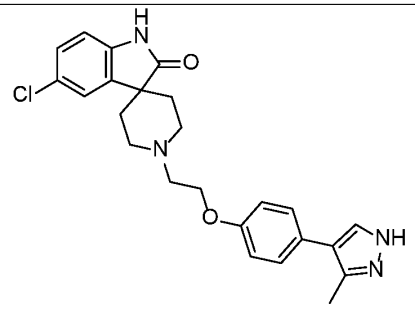
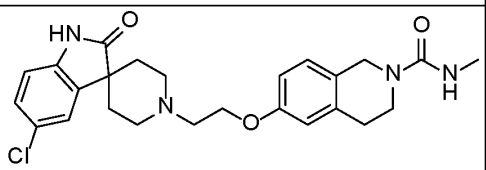
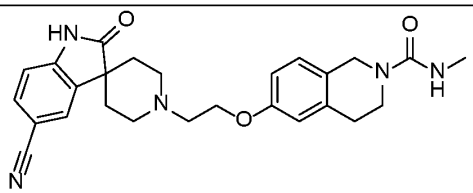
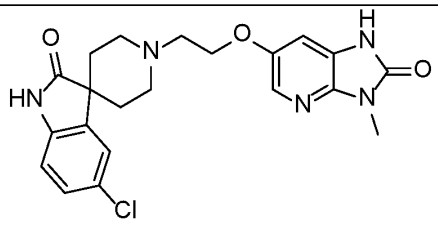
		dihydrospiro[indole-3,4'-piperidin]-2-one
225		5-chloro-1'-[2-(4-{[1-(hydroxymethyl)cyclopropyl]sulfonyl}phenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
226		1-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzenesulfonyl]-N-methylcyclopropane-1-carboxamide
227		1-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzenesulfonyl]-N,N-dimethylcyclopropane-1-carboxamide

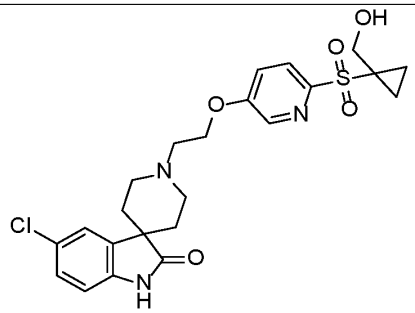
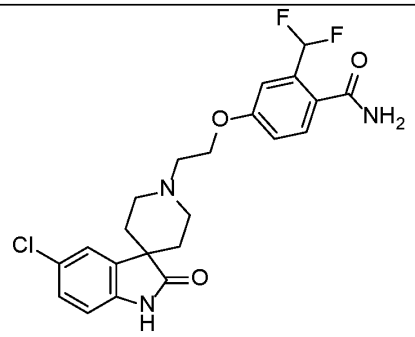
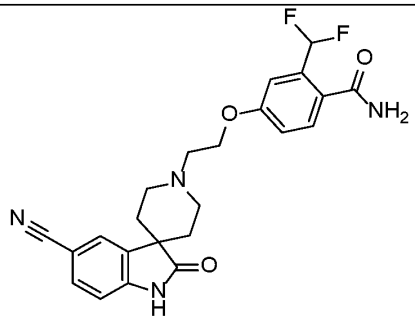
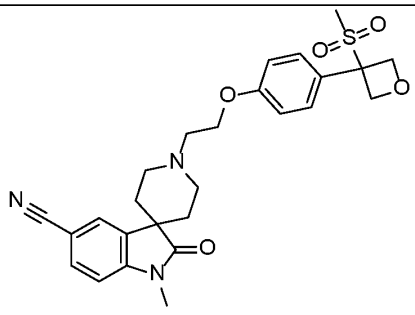
228		1'-[2-(4-{[1-(azetidine-1-carbonyl)cyclopropyl]sulfonyl}phenoxy)ethyl]-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
229		4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluoro-N-methylbenzamide
230		4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluoro-N,N-dimethylbenzamide
231		5-chloro-1'-{2-[3-fluoro-4-(morpholine-4-carbonyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

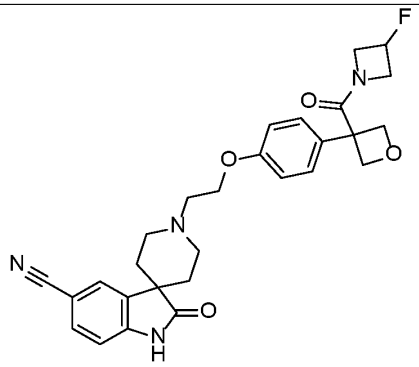
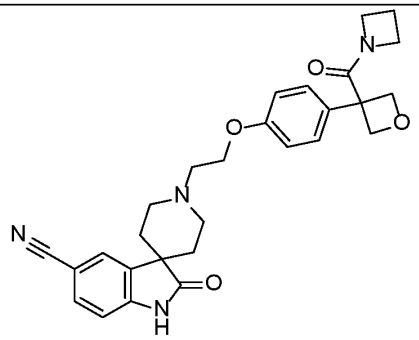
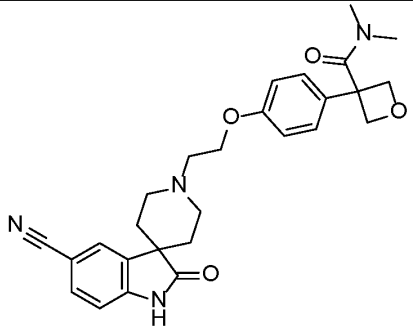
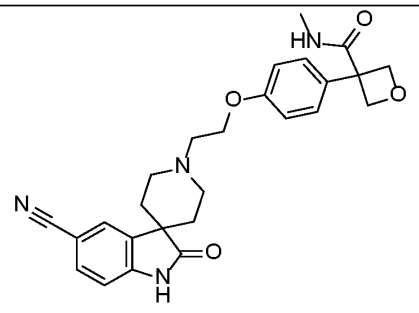
232		4-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzoyl]-1λ⁶-thiomorpholine-1,1-dione
233		5-chloro-1'-{2-[3-fluoro-4-(3-methanesulfonylazetidine-1-carbonyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
234		1'-{2-[4-(azetidine-1-carbonyl)-3-fluorophenoxy]ethyl}-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
235		5-chloro-1'-{2-[3-fluoro-4-(3-hydroxyazetidine-1-carbonyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

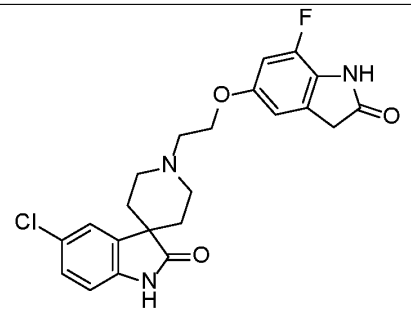
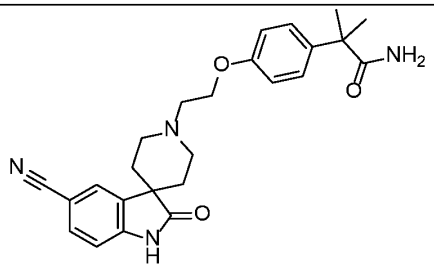
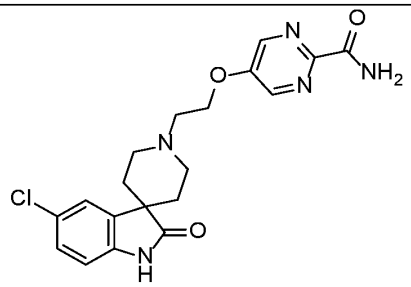
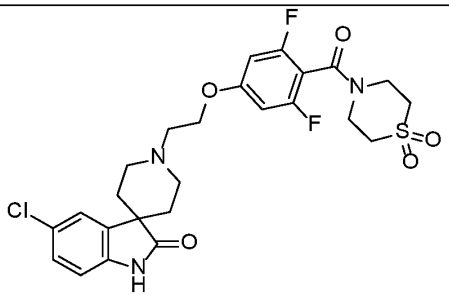
236		1'-{2-[4-(3-aminoazetidine-1-carbonyl)-3-fluorophenoxy]ethyl}-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
237		N-{1-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzoyl]azetidin-3-yl}methanesulfonamide
238		4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzamide
239		6-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzoyl]-2λ⁶-thia-6-azaspiro[3.3]heptane-2,2-dione

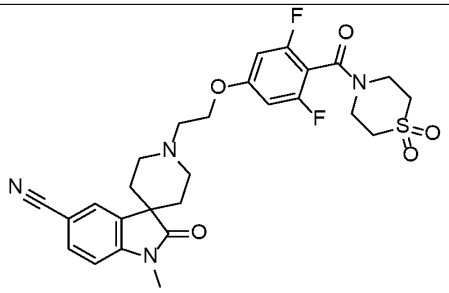
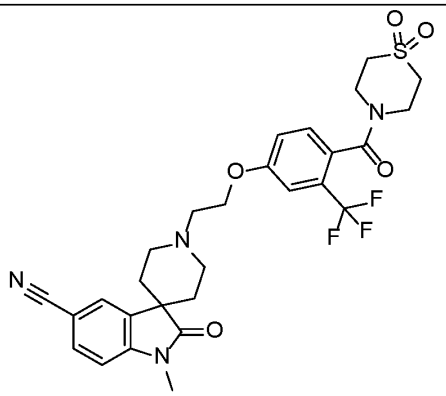
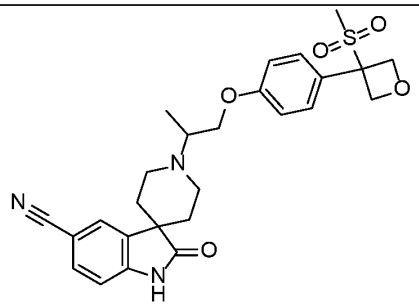
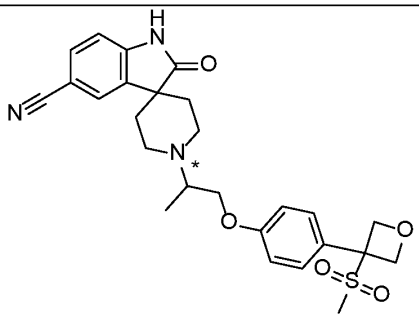
240		4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-(1,1-dioxo-1λ⁶-thian-4-yl)-2-fluorobenzamide
241		4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-(1,1-dioxo-1λ⁶-thiolan-3-yl)-2-fluorobenzamide
242		4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-[(3S) or (3R)-1,1-dioxo-1λ⁶-thiolan-3-yl]-2-fluorobenzamide
243		4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-[(3R) or (3S)-1,1-dioxo-1λ⁶-thiolan-3-yl]-2-fluorobenzamide

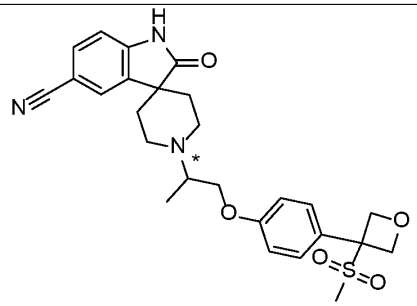
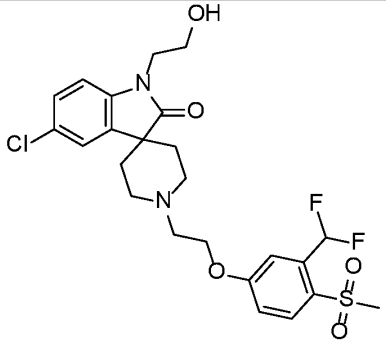
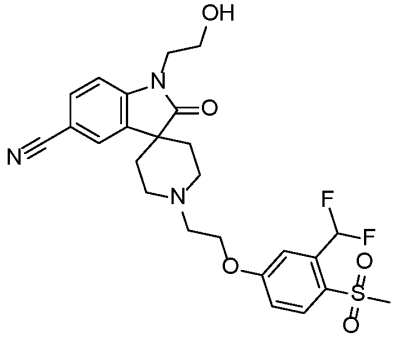
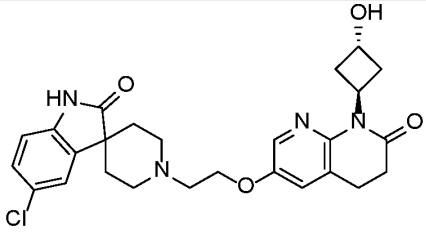
244		5-chloro-1'-{2-[4-(3-methyl-1H-pyrazol-4-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
245		6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-methyl-1,2,3,4-tetrahydroisoquinoline-2-carboxamide
246		6-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-methyl-1,2,3,4-tetrahydroisoquinoline-2-carboxamide
247		5-chloro-1'-[2-({3-methyl-2-oxo-1H,2H,3H-imidazo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

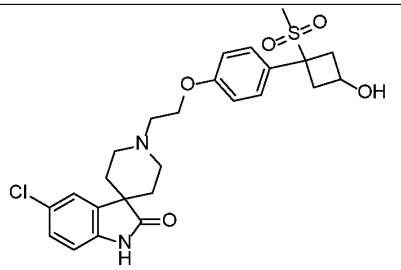
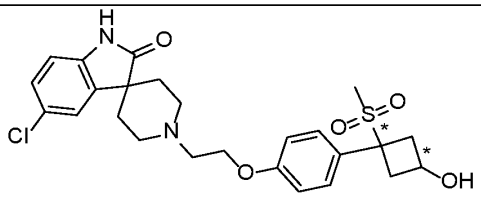
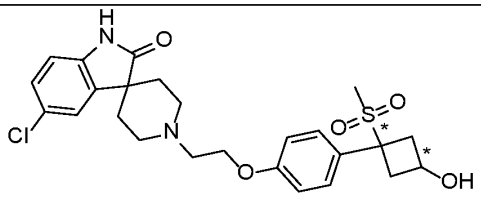
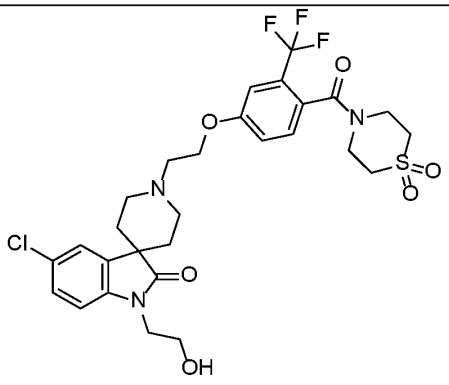
248		5-chloro-1'-{2-[(6-{[1-(hydroxymethyl)cyclopropyl]sulfonyl}pyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
249		4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(difluoromethyl)benzamide
250		4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(difluoromethyl)benzamide
251		1'-{2-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile

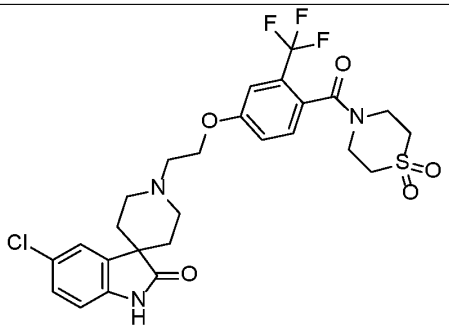
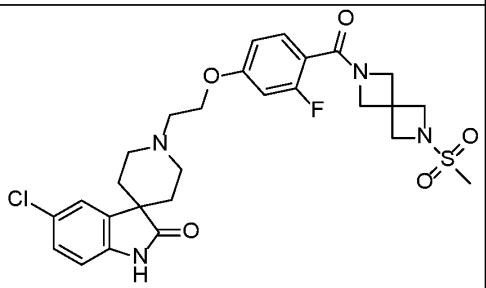
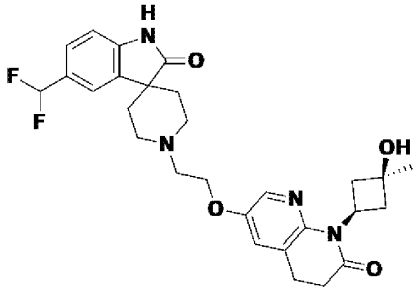
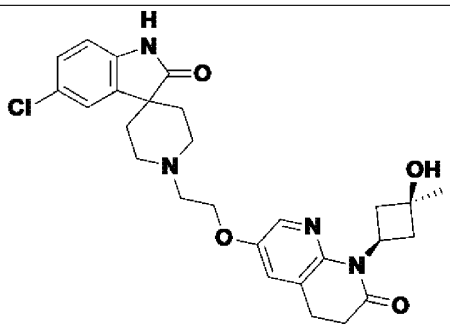
252		1'-(2-{4-[3-(3-fluoroazetidine-1-carbonyl)oxetan-3-yl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
253		1'-(2-{4-[3-(azetidine-1-carbonyl)oxetan-3-yl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
254		3-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-N,N-dimethyloxetane-3-carboxamide
255		3-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-N-methyloxetane-3-carboxamide

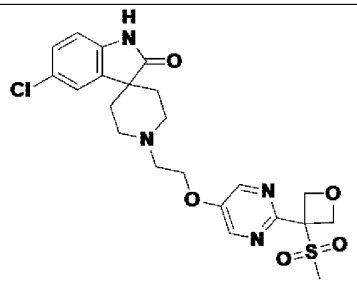
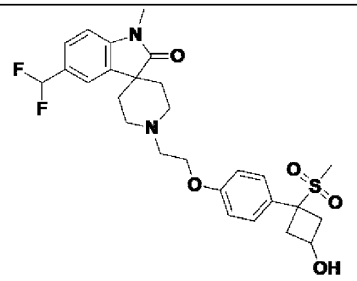
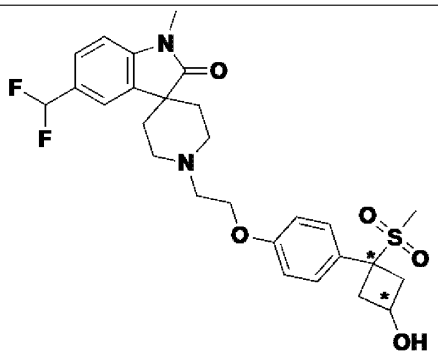
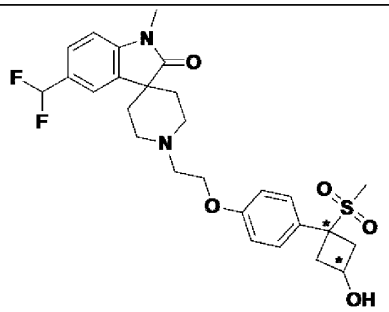
256		5-chloro-1'-{2-[(7-fluoro-2-oxo-2,3-dihydro-1H-indol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
257		2-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-2-methylpropanamide
258		5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)pyrimidine-2-carboxamide
259		4-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,6-difluorobenzoyl]-1λ⁶-thiomorpholine-1,1-dione

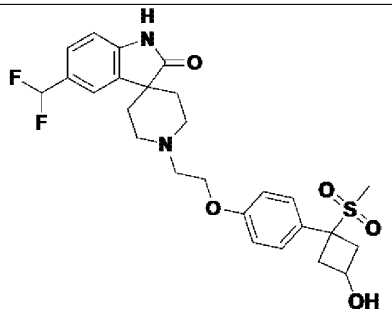
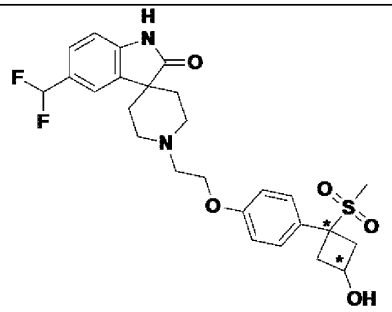
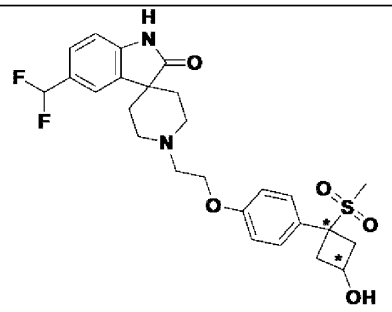
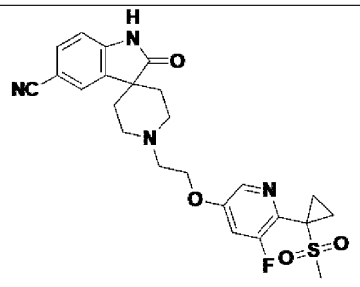
260		1'-{2-[4-(1,1-dioxo-1λ⁶-thiomorpholine-4-carbonyl)-3,5-difluorophenoxy]ethyl}-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
261		1'-{2-[4-(1,1-dioxo-1λ⁶-thiomorpholine-4-carbonyl)-3-(trifluoromethyl)phenoxy]ethyl}-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
262		1'-{1-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
263		(S) or (R)-1'-{1-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile

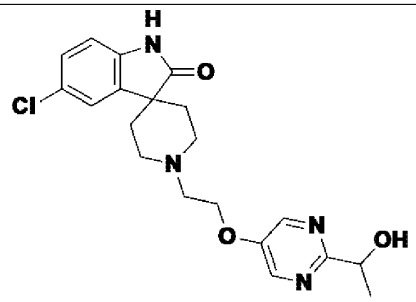
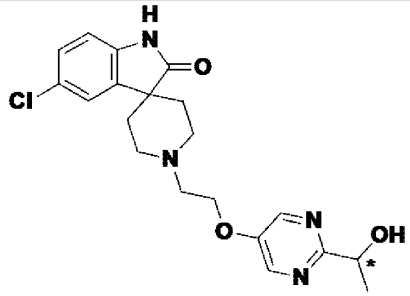
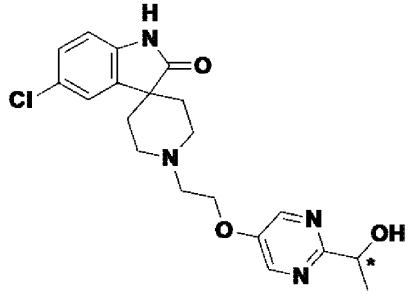
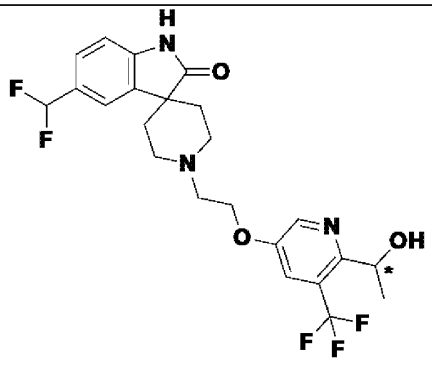
264		(R) or (S)-1'-{1-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
265		5-chloro-1'-{2-[3-(difluoromethyl)-4-methanesulfonylphenoxy]ethyl}-1-(2-hydroxyethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
266		1'-{2-[3-(difluoromethyl)-4-methanesulfonylphenoxy]ethyl}-1-(2-hydroxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
267		5-chloro-1'-[2-({7-oxo-8-[(trans)-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

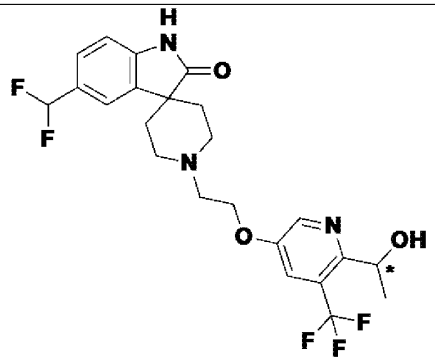
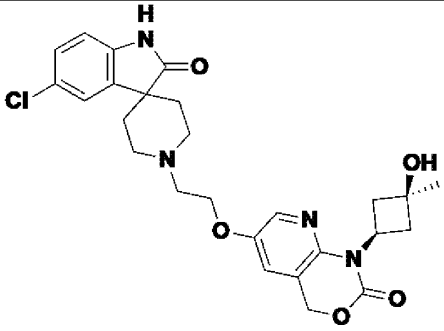
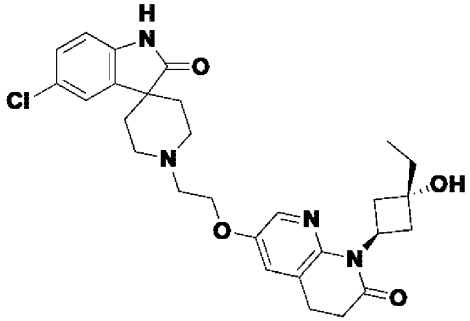
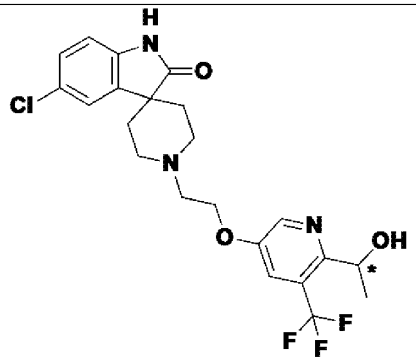
268		5-chloro-1'-{2-[4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
269		5-chloro-1'-(2-{4-[(cis) or (trans)-3-hydroxy-1-methanesulfonylcyclobutyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
270		5-chloro-1'-(2-{4-[(trans) or (cis)-3-hydroxy-1-methanesulfonylcyclobutyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
271		4-(4-{2-[5-chloro-1-(2-hydroxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl]ethoxy}-2-(trifluoromethyl)benzoyl)-1λ⁶-thiomorpholine-1,1-dione

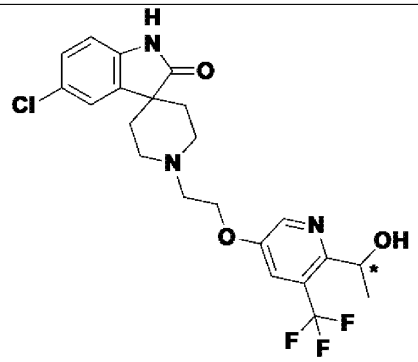
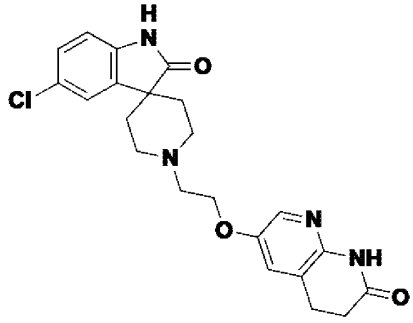
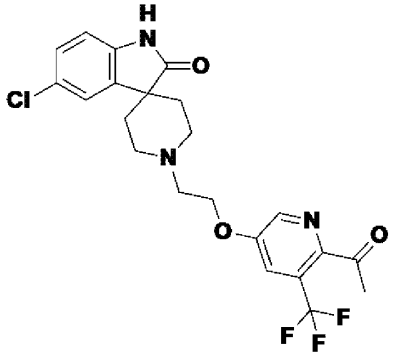
272		4-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(trifluoromethyl)benzoyl]-1λ⁶-thiomorpholine-1,1-dione
273		5-chloro-1'-[2-(3-fluoro-4-{6-methanesulfonyl-2,6-diazaspiro[3.3]heptane-2-carbonyl}phenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
274		5-(difluoromethyl)-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
275		5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

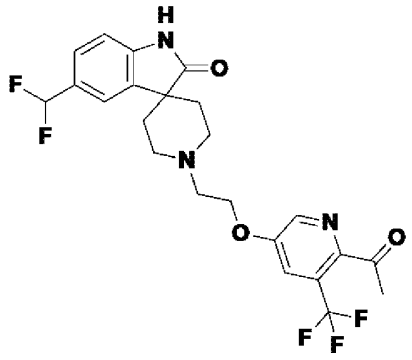
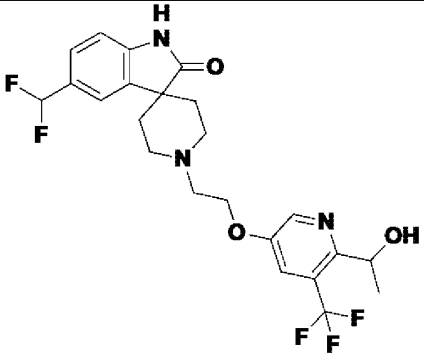
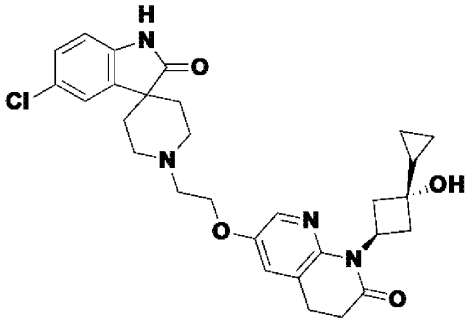
276		5-chloro-1'-(2-{[2-(3-methanesulfonyloxetan-3-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
277		5-(difluoromethyl)-1'-{2-[4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenoxy]ethyl}-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
278		5-(difluoromethyl)-1-methyl-1'-(2-{4-[(*cis*) or (*trans*)-3-hydroxy-1-methanesulfonylcyclobutyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
279		5-(difluoromethyl)-1-methyl-1'-(2-{4-[(*trans*) or (*cis*)-3-hydroxy-1-methanesulfonylcyclobutyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

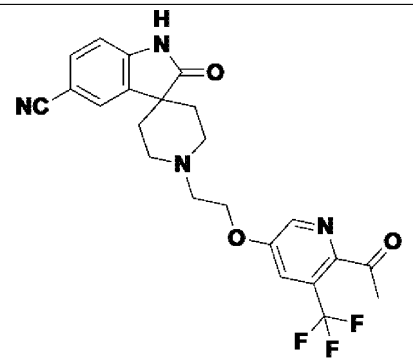
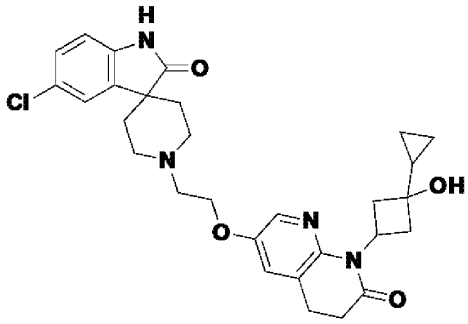
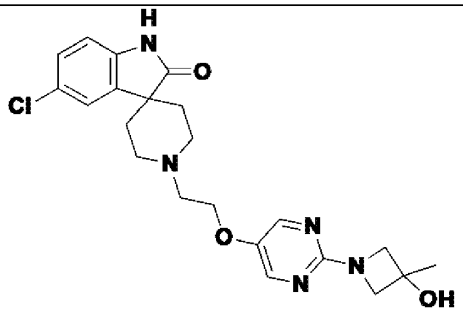
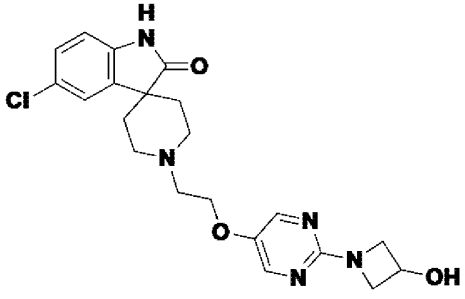
280		5-(difluoromethyl)-1'-{2-[4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
281		5-(difluoromethyl)-1'-(2-{4-[(*cis*) or (*trans*)-3-hydroxy-1-methanesulfonylcyclobutyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
282		5-(difluoromethyl)-1'-(2-{4-[(*trans*) or (*cis*)-3-hydroxy-1-methanesulfonylcyclobutyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
283		1'-(2-{[5-fluoro-6-(1-methanesulfonylcyclopropyl)pyridin-3-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile

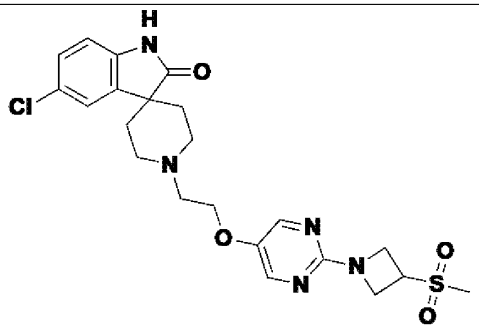
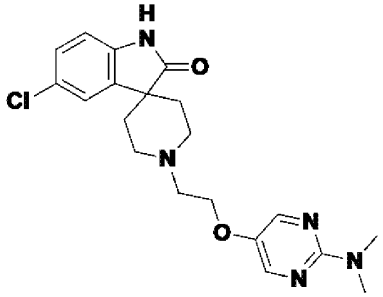
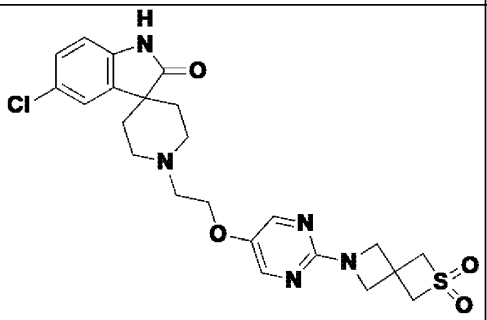
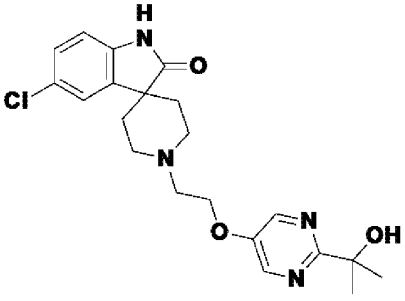
284		5-chloro-1'-(2-{[2-(1-hydroxyethyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
285		5-chloro-1'-[2-({2-[(1*S*) or (1*R*)-1-hydroxyethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
286		5-chloro-1'-[2-({2-[(1*R*) or (1*S*)-1-hydroxyethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
287		5-(difluoromethyl)-1'-[2-({6-[(1*S*) or (1*R*)-1-hydroxyethyl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

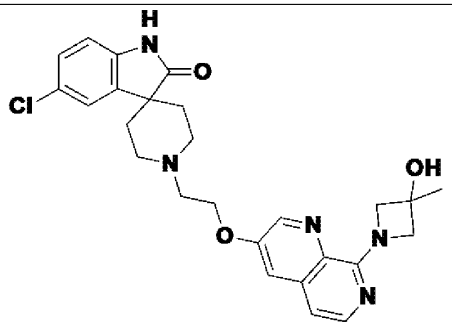
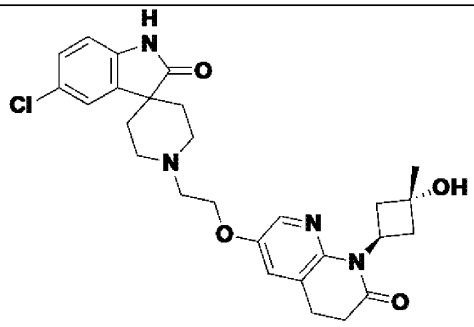
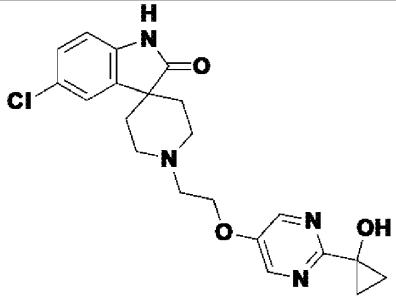
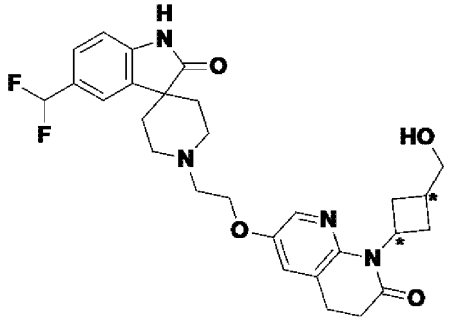
288		5-(difluoromethyl)-1'-[2-({6-[(1*R*) or (1*S*)-1-hydroxyethyl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
289		5-chloro-1'-[2-({2-oxo-1-*[(cis)*-3-hydroxy-3-methylcyclobutyl]-1H,2H,4H-pyrido[2,3-d][1,3]oxazin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
290		5-chloro-1'-[2-({7-oxo-8-*[(trans)*-3-ethyl-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
291		5-chloro-1'-[2-({6-[(1*S*) or (1*R*)-1-hydroxyethyl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

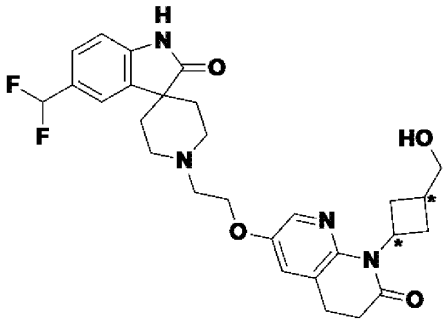
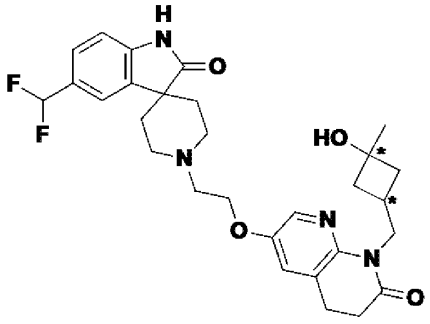
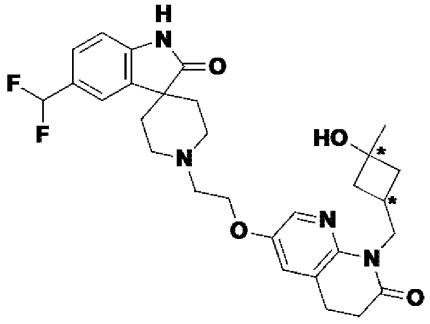
292		5-chloro-1'-[2-({6-[(1*R*) or (1*S*)-1-hydroxyethyl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
293		5-chloro-1'-{2-[(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
294		1'-(2-{[6-acetyl-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

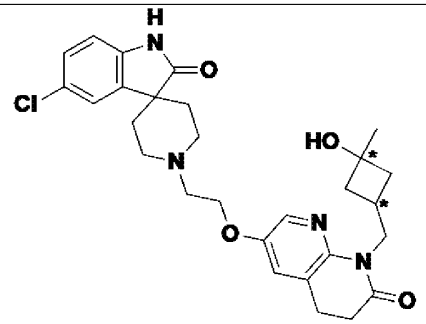
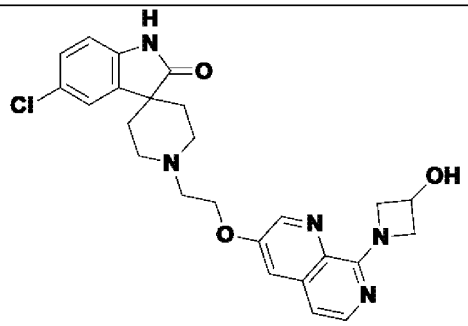
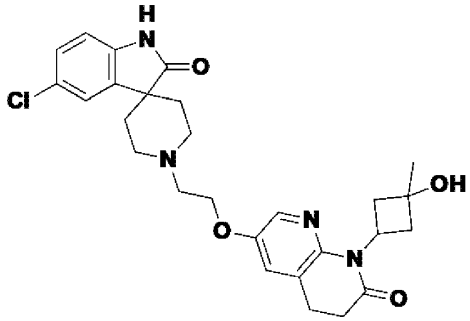
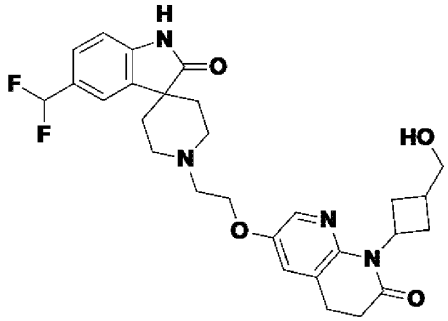
295		1'-(2-{[6-acetyl-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-5-(difluoromethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
296		5-(difluoromethyl)-1'-(2-{[6-(1-hydroxyethyl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
297		5-chloro-1'-[2-({7-oxo-8-*[(trans)*-3-cyclopropyl-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

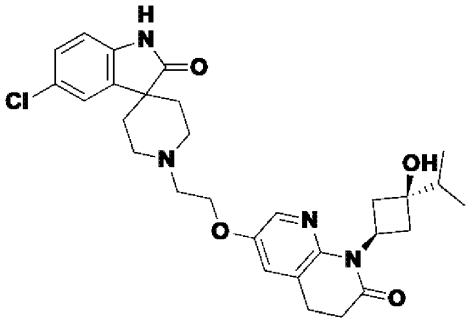
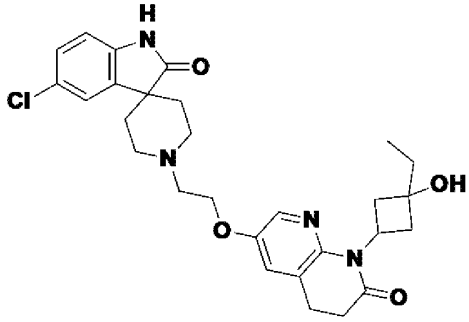
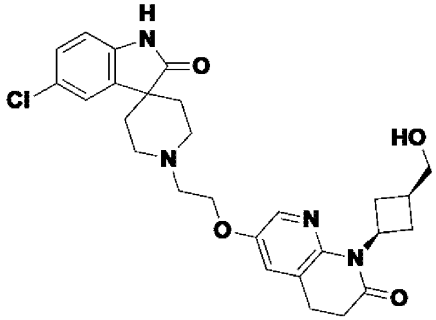
298		1'-(2-{[6-acetyl-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
299		5-chloro-1'-(2-{[8-(3-cyclopropyl-3-hydroxycyclobutyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
300		5-chloro-1'-(2-{[2-(3-hydroxy-3-methylazetidin-1-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
301		5-chloro-1'-(2-{[2-(3-hydroxyazetidin-1-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

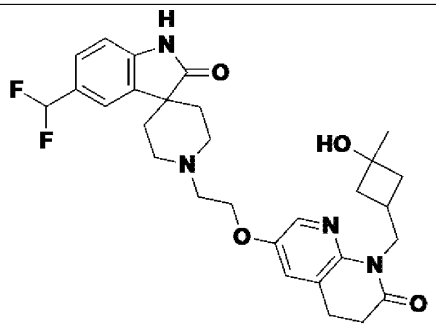
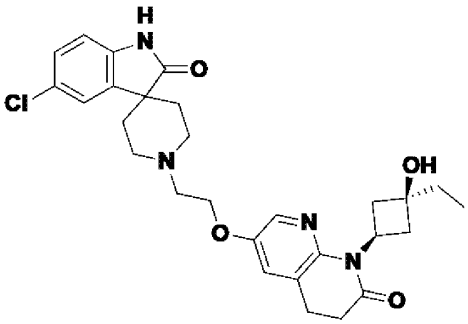
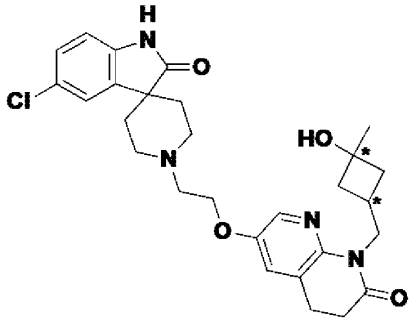
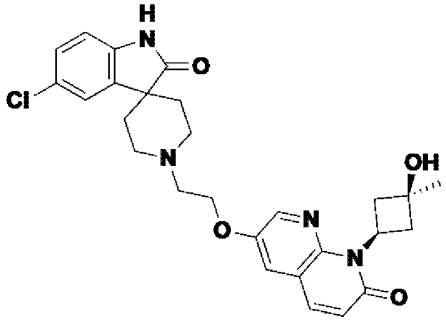
302		5-chloro-1'-(2-{[2-(3-methanesulfonylazetidin-1-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
303		5-chloro-1'-(2-{[2-(dimethylamino)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
304		6-[5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)pyrimidin-2-yl]-2λ⁶-thia-6-azaspiro[3.3]heptane-2,2-dione
305		5-chloro-1'-(2-{[2-(2-hydroxypropan-2-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

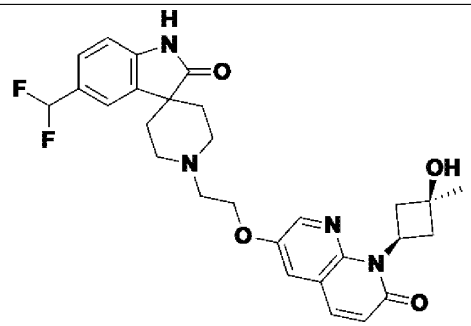
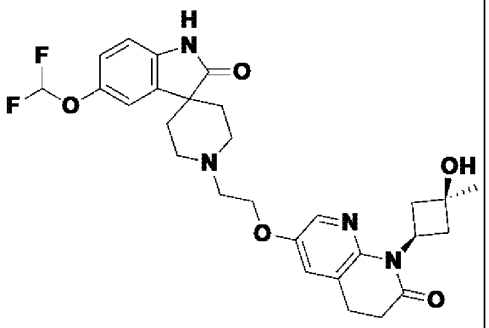
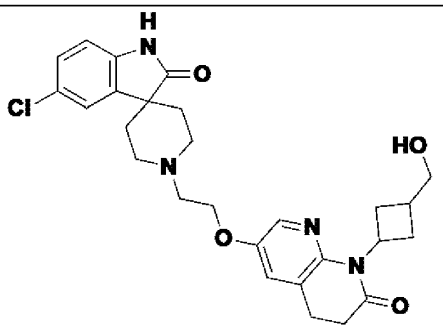
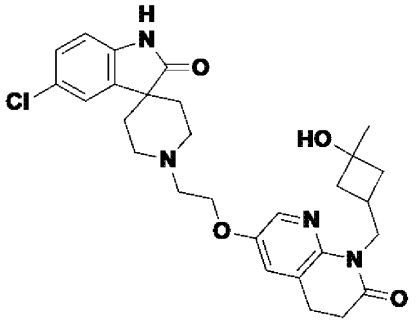
306		5-chloro-1'-(2-{[8-(3-hydroxy-3-methylazetidin-1-yl)-1,7-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
307		5-chloro-1'-[2-({7-oxo-8-*[(trans)*-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
308		5-chloro-1'-(2-{[2-(1-hydroxycyclopropyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
309		5-(difluoromethyl)-1'-[2-({7-oxo-8-*[(cis)* or *(trans)*-3-(hydroxymethyl)cyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

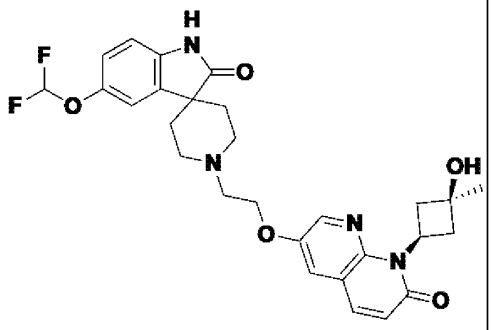
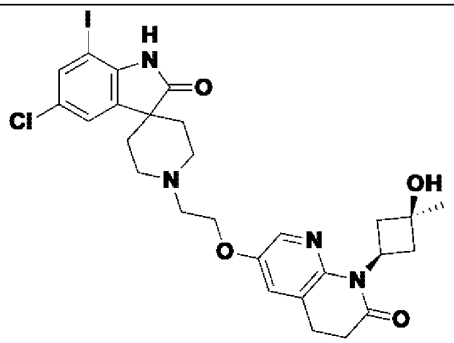
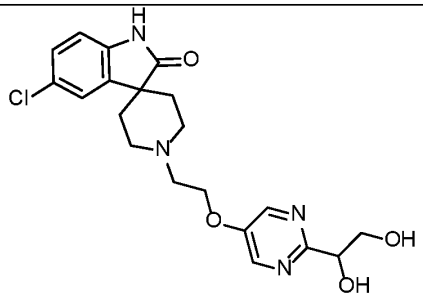
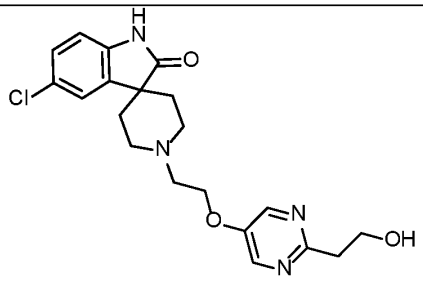
310		5-(difluoromethyl)-1'-[2-({7-oxo-8-*[(trans)* or *(cis)*-3-(hydroxymethyl)cyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
311		5-(difluoromethyl)-1'-{2-[(7-oxo-8-*{[(cis)* or *(trans)*-3-hydroxy-3-methylcyclobutyl]methyl}-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
312		5-(difluoromethyl)-1'-{2-[(7-oxo-8-*{[(trans)* or *(cis)*-3-hydroxy-3-methylcyclobutyl]methyl}-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

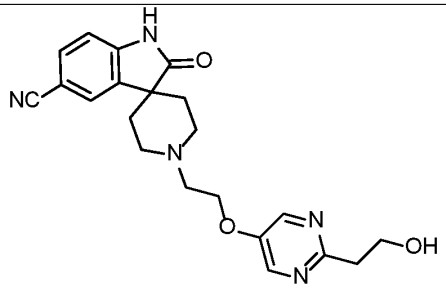
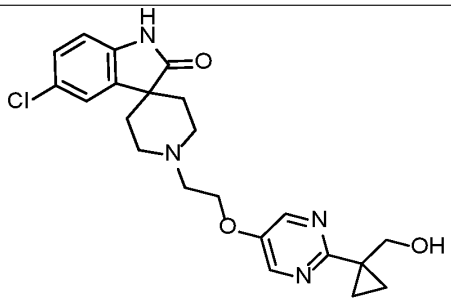
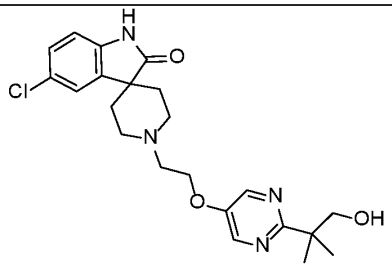
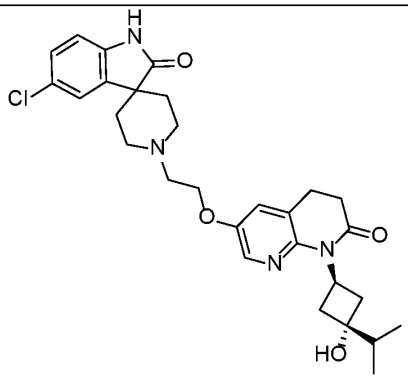
313		5-chloro-1'-{2-[(7-oxo-8-{[(*cis)* or *(trans)*-3-hydroxy-3-methylcyclobutyl]methyl}-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
314		5-chloro-1'-(2-{[8-(3-hydroxyazetidin-1-yl)-1,7-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
315		5-chloro-1'-(2-{[8-(3-hydroxy-3-methylcyclobutyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
316		5-(difluoromethyl)-1'-[2-({8-[3-(hydroxymethyl)cyclobutyl]-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

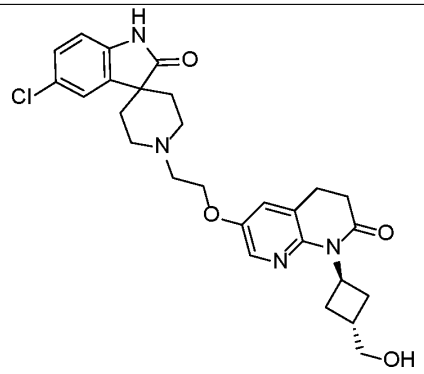
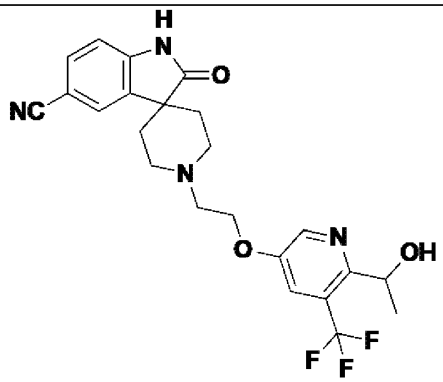
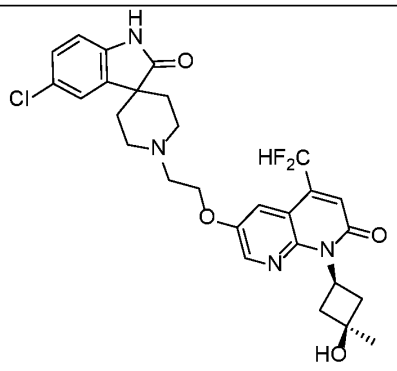
317		5-chloro-1'-[2-({7-oxo-8-*[(cis)*-3-hydroxy-3-(propan-2-yl)cyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
318		5-chloro-1'-(2-{[8-(3-ethyl-3-hydroxycyclobutyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
319		5-chloro-1'-[2-({7-oxo-8-*[(cis)*-3-(hydroxymethyl)cyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

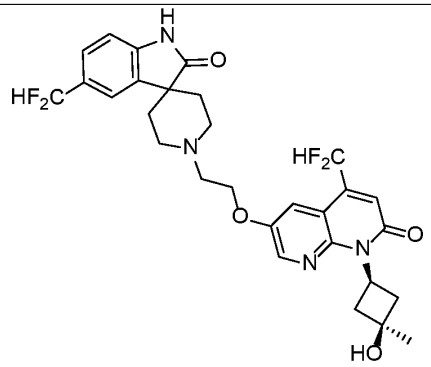
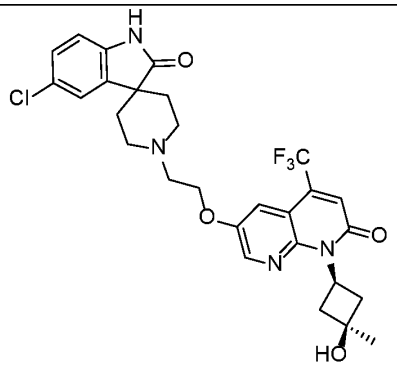
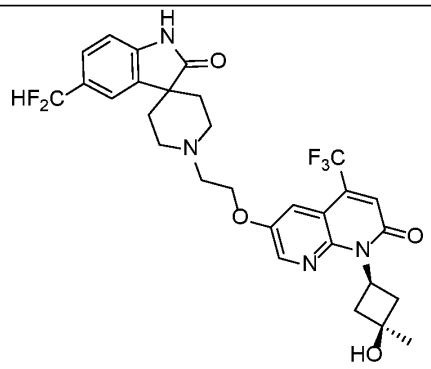
320		5-(difluoromethyl)-1'-[2-({8-[(3-hydroxy-3-methylcyclobutyl)methyl]-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
321		5-chloro-1'-[2-({7-oxo-8-*[(cis)*-3-ethyl-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
322		5-chloro-1'-{2-[(7-oxo-8-{[(*trans)* or (*cis*)-3-hydroxy-3-methylcyclobutyl]methyl}-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
323		5-chloro-1'-[2-({7-oxo-8-*[(cis)*-3-hydroxy-3-methylcyclobutyl]-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

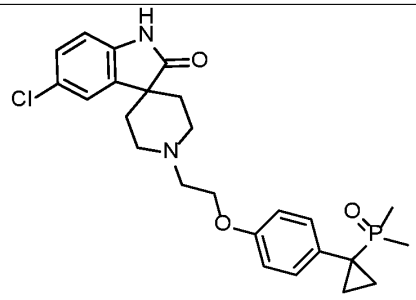
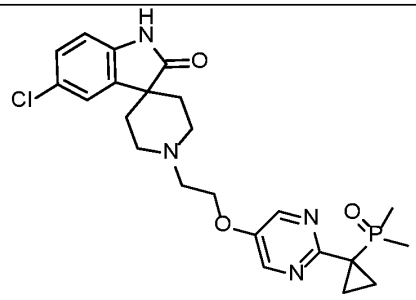
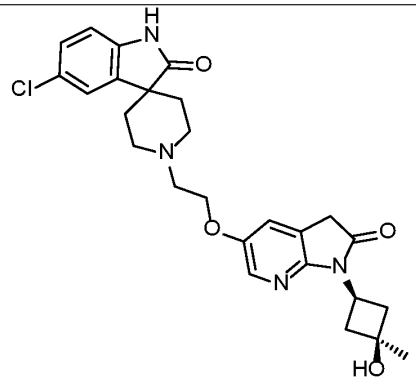
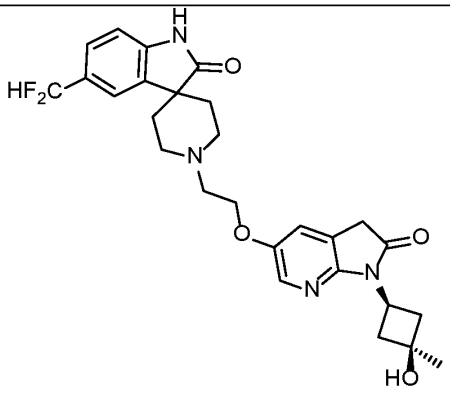
324		5-(difluoromethyl)-1'-[2-({7-oxo-8-*[(cis)*-3-hydroxy-3-methylcyclobutyl]-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
325		5-(difluoromethoxy)-1'-[2-({7-oxo-8-*[(cis)*-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
326		5-chloro-1'-[2-({8-[3-(hydroxymethyl)cyclobutyl]-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
327		5-chloro-1'-[2-({8-[(3-hydroxy-3-methylcyclobutyl)methyl]-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

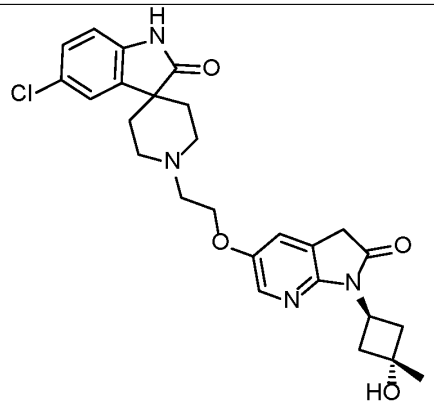
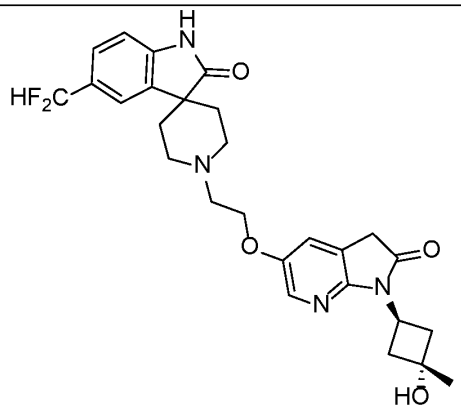
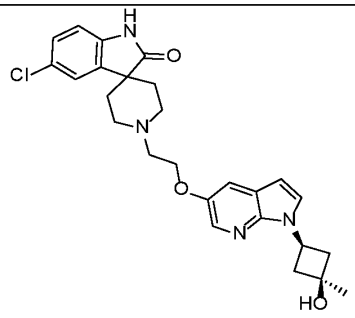
328		5-(difluoromethoxy)-1'-[2-({7-oxo-8-*[(cis)*-3-hydroxy-3-methylcyclobutyl]-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
329		5-chloro-7-iodo-1'-[2-({7-oxo-8-*[(cis)*-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
330		5-chloro-1'-(2-{[2-(1,2-dihydroxyethyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
331		5-chloro-1'-(2-{[2-(2-hydroxyethyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

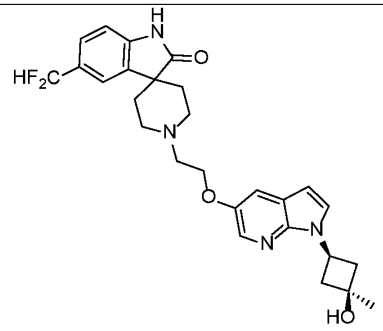
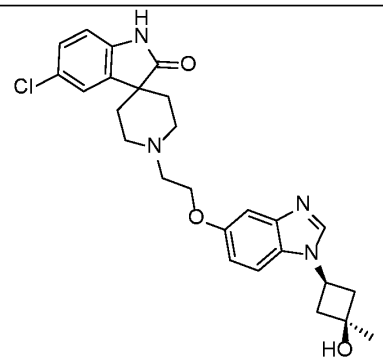
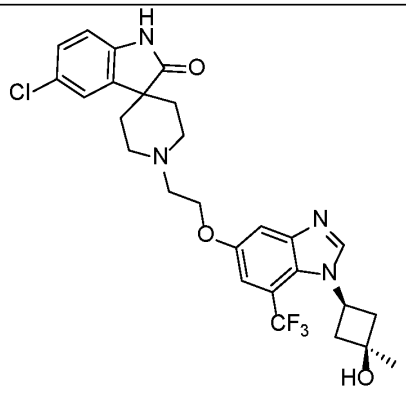
332		1'-(2-{[2-(2-hydroxyethyl)pyrimidin-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
333		5-chloro-1'-[2-({2-[1-(hydroxymethyl)cyclopropyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
334		5-chloro-1'-(2-{[2-(1-hydroxy-2-methylpropan-2-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
335		5-chloro-1'-[2-({7-oxo-8-[(*trans*)-3-hydroxy-3-(propan-2-yl)cyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

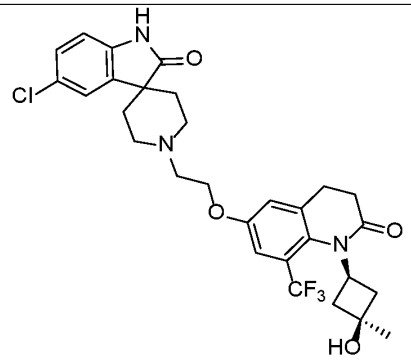
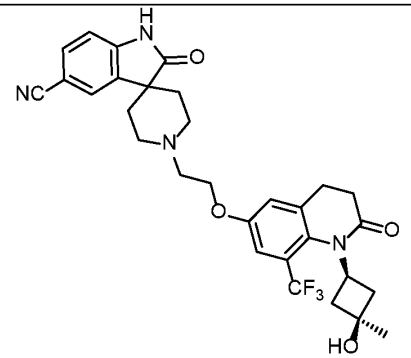
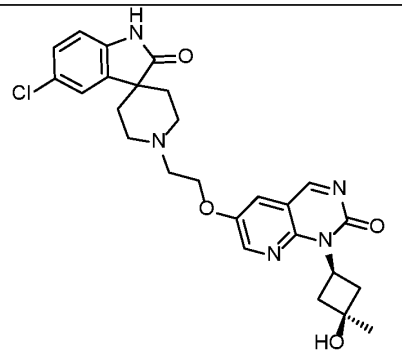
336		5-chloro-1'-[2-({7-oxo-8-[(*trans*)-3-(hydroxymethyl)cyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
338		1'-(2-{[6-(1-hydroxyethyl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
339		5-chloro-1'-(2-{[5-(difluoromethyl)-7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7,8-dihydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

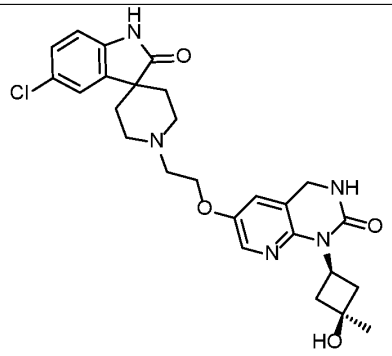
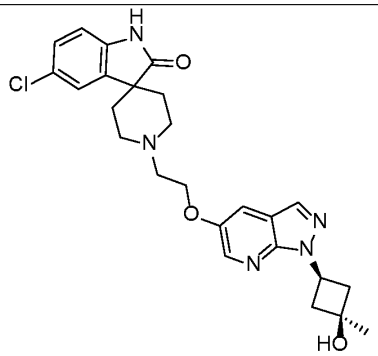
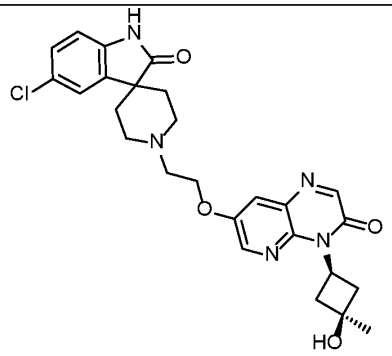
340		5-(difluoromethyl)-1'-(2-{[5-(difluoromethyl)-7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7,8-dihydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
341		5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5-(trifluoromethyl)-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
342		5-(difluoromethyl)-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5-(trifluoromethyl)-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

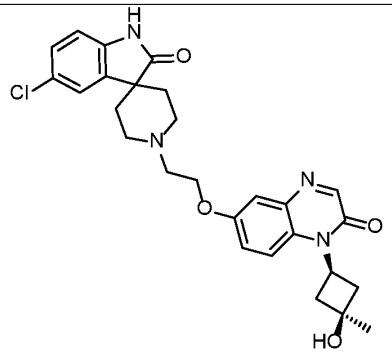
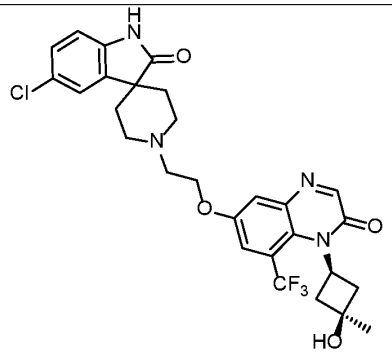
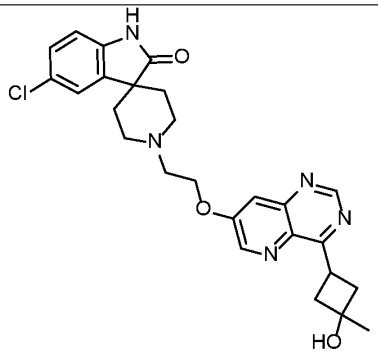
343		5-chloro-1'-(2-{4-[1-(dimethylphosphoryl)cyclopropyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
344		5-chloro-1'-[2-({2-[1-(dimethylphosphoryl)cyclopropyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
345		5-chloro-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
346		5-(difluoromethyl)-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

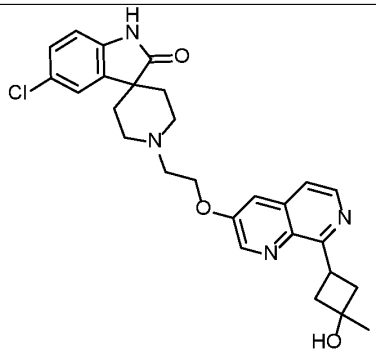
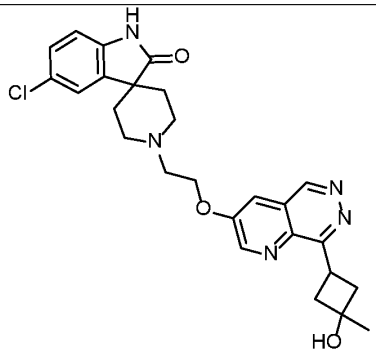
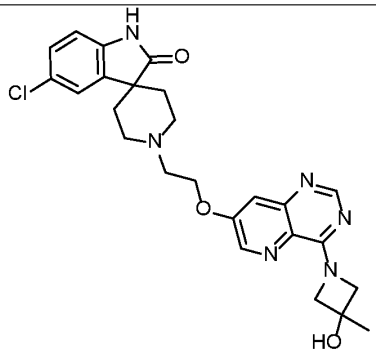
347		5-chloro-1'-[2-({2-oxo-1-[(*trans*)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
348		5-(difluoromethyl)-1'-[2-({2-oxo-1-[(*trans*)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
349		5-chloro-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

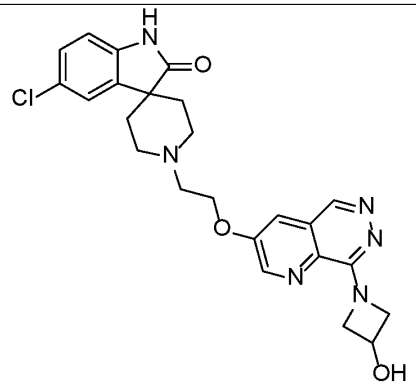
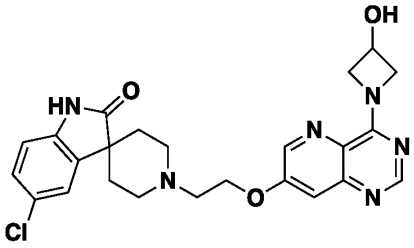
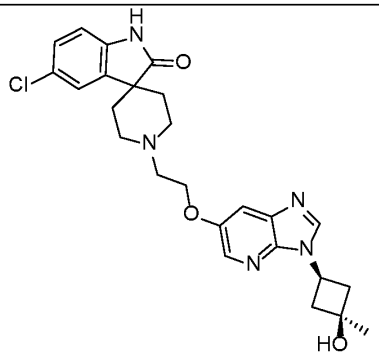
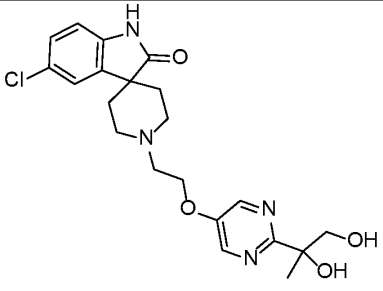
350		5-(difluoromethyl)-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
351		5-chloro-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
352		5-chloro-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

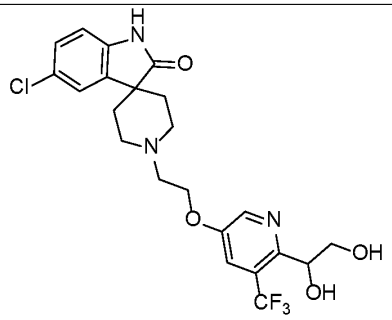
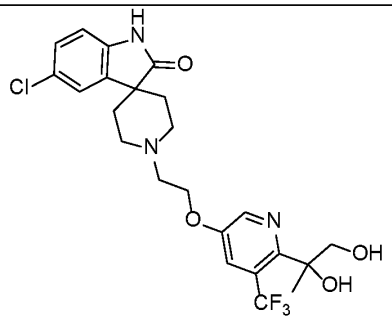
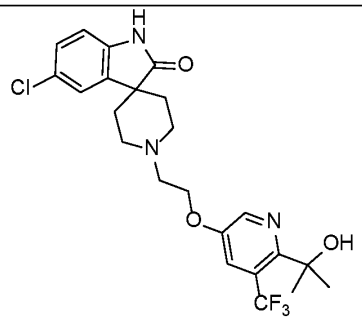
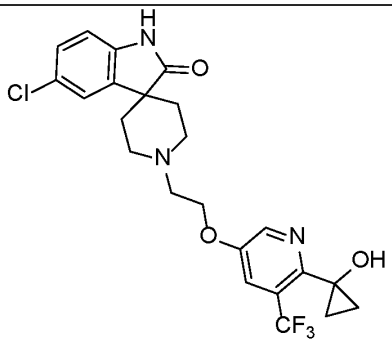
353		5-chloro-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
354		2-oxo-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
355		5-chloro-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H,2H-pyrido[2,3-d]pyrimidin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

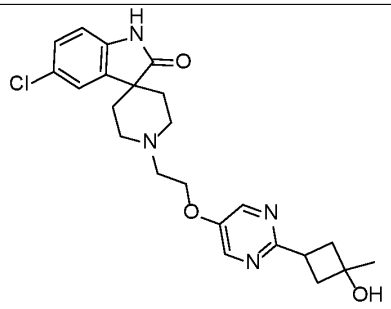
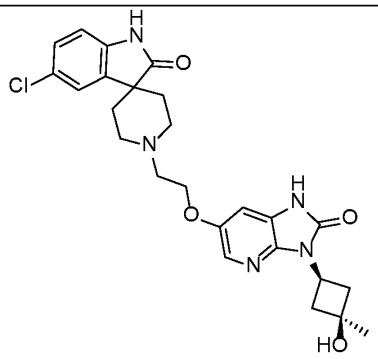
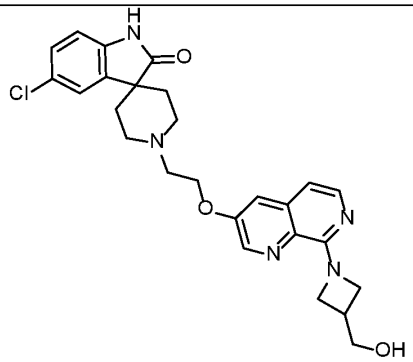
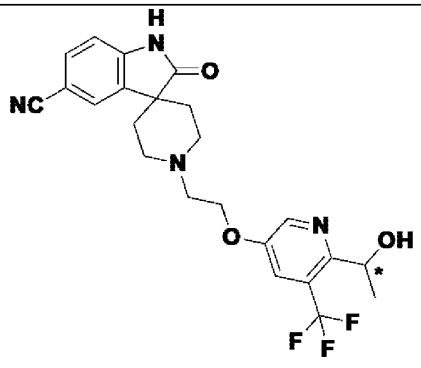
356		5-chloro-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H,4H-pyrido[2,3-d]pyrimidin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
357		5-chloro-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-pyrazolo[3,4-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
358		5-chloro-1'-[2-({3-oxo-4-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-3H,4H-pyrido[2,3-b]pyrazin-7-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

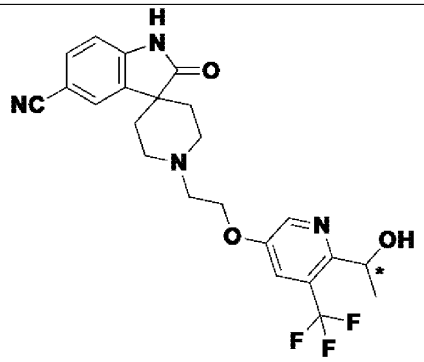
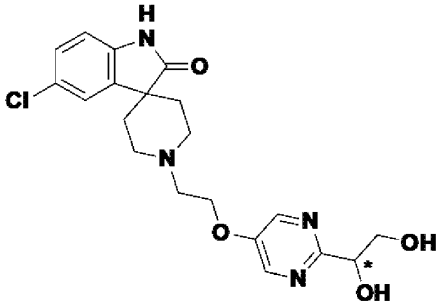
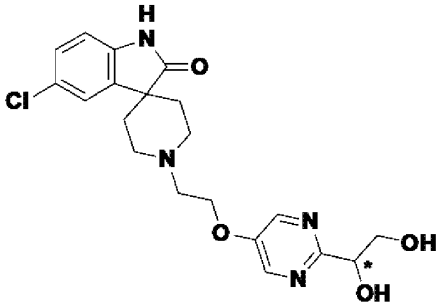
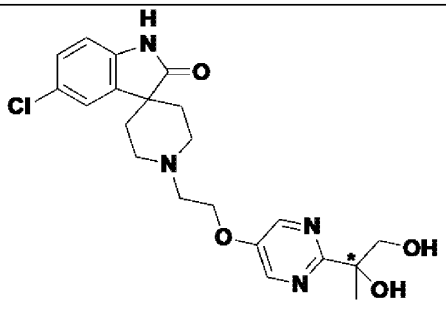
359		5-chloro-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1,2-dihydroquinoxalin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
360		5-chloro-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-8-(trifluoromethyl)-1,2-dihydroquinoxalin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
361		5-chloro-1'-(2-{[4-(3-hydroxy-3-methylcyclobutyl)pyrido[3,2-d]pyrimidin-7-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

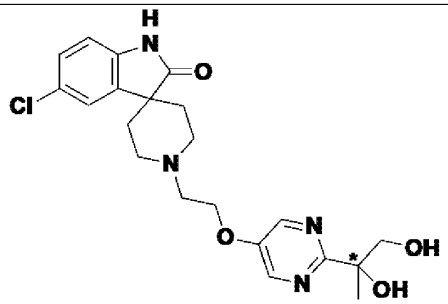
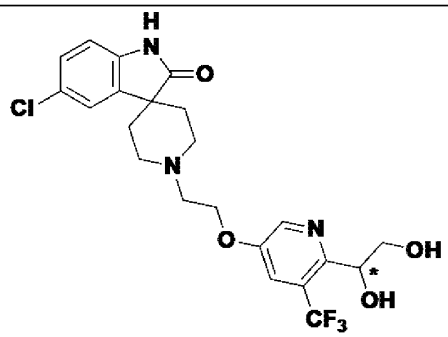
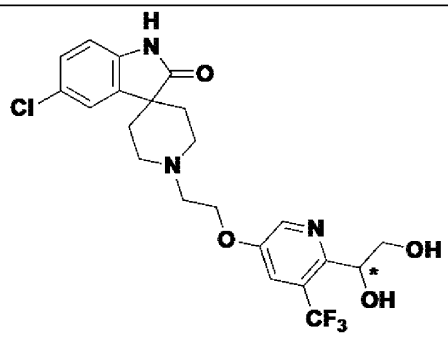
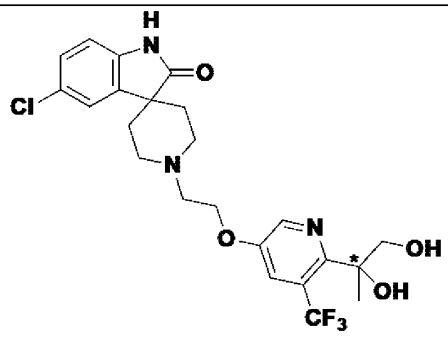
362		5-chloro-1'-(2-{[8-(3-hydroxy-3-methylcyclobutyl)-1,7-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
363		5-chloro-1'-(2-{[8-(3-hydroxy-3-methylazetidin-1-yl)pyrido[2,3-d]pyridazin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
364		5-chloro-1'-(2-{[4-(3-hydroxy-3-methylazetidin-1-yl)pyrido[3,2-d]pyrimidin-7-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

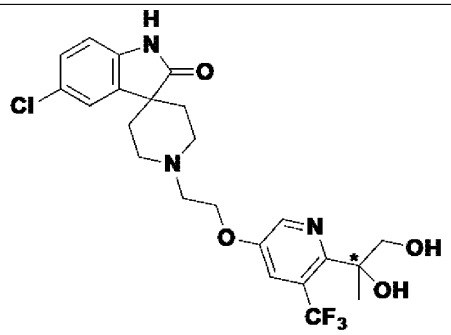
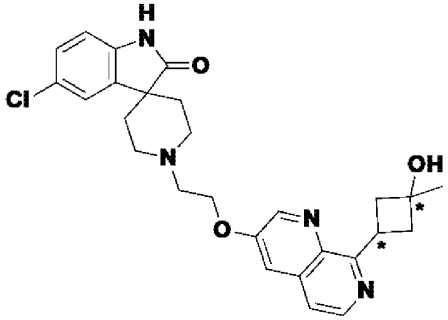
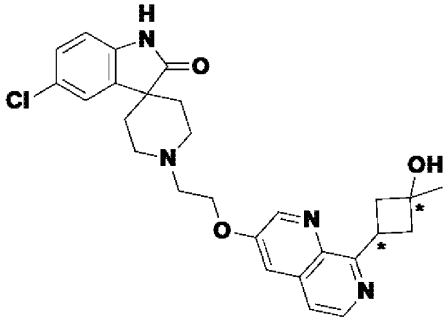
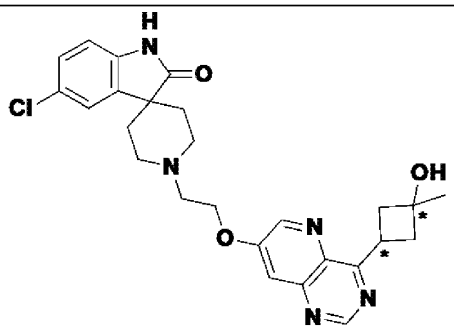
365		5-chloro-1'-(2-{[8-(3-hydroxyazetidin-1-yl)pyrido[2,3-d]pyridazin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
366		5-chloro-1'-(2-{[4-(3-hydroxyazetidin-1-yl)pyrido[3,2-d]pyrimidin-7-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
367		5-chloro-1'-[2-({3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-3H-imidazo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
368		5-chloro-1'-(2-{[2-(1,2-dihydroxypropan-2-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

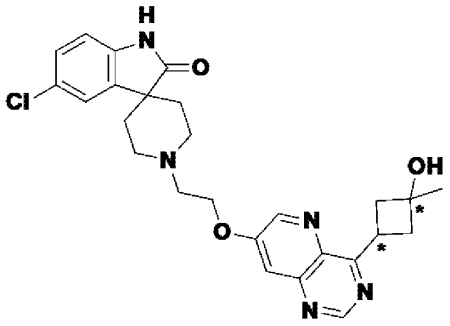
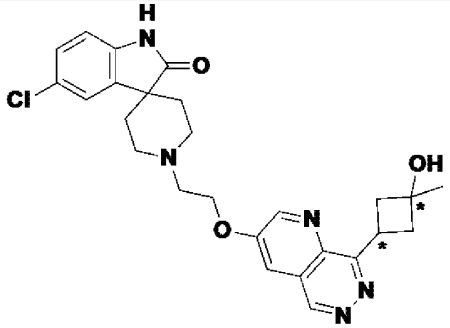
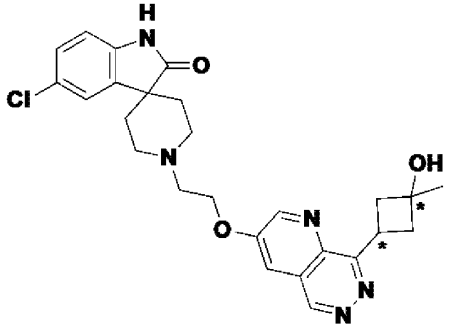
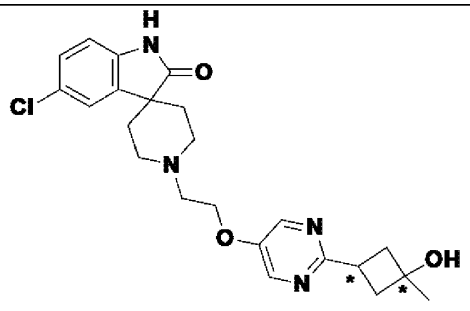
369		5-chloro-1'-(2-((6-(1,2-dihydroxyethyl)-5-(trifluoromethyl)pyridin-3-yl)oxy)ethyl)spiro[indoline-3,4'-piperidin]-2-one
370		5-chloro-1'-(2-{[6-(1,2-dihydroxypropan-2-yl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
371		5-chloro-1'-(2-{[6-(2-hydroxypropan-2-yl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
372		5-chloro-1'-(2-{[6-(1-hydroxycyclopropyl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

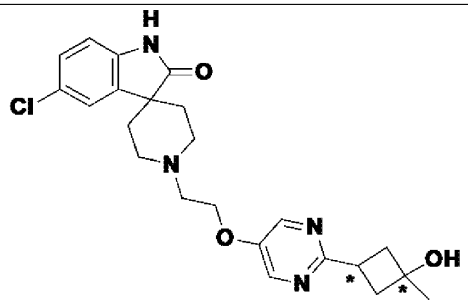
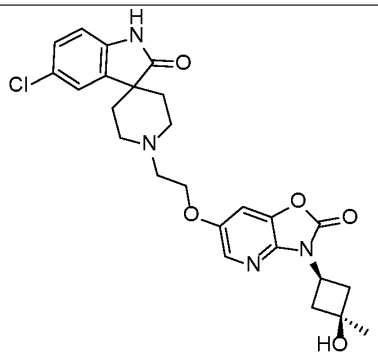
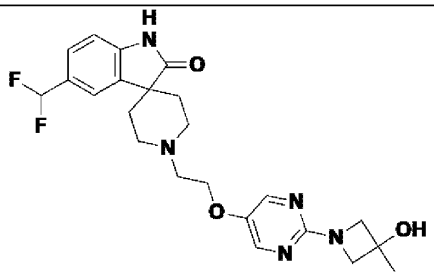
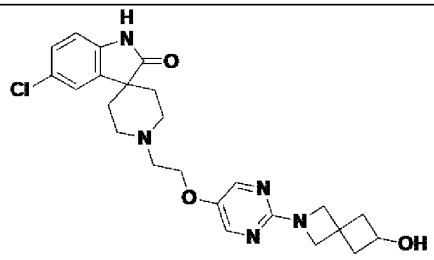
373		5-chloro-1'-(2-{[2-(3-hydroxy-3-methylcyclobutyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
374		5-chloro-1'-[2-({2-oxo-3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H-imidazo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
375		5-chloro-1'-[2-({8-[3-(hydroxymethyl)azetidin-1-yl]-1,7-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
376		1'-[2-({6-[(1*S*) or (1*R*) -1-hydroxyethyl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile

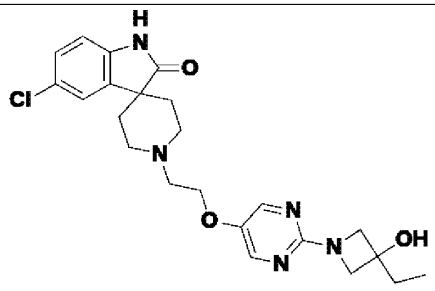
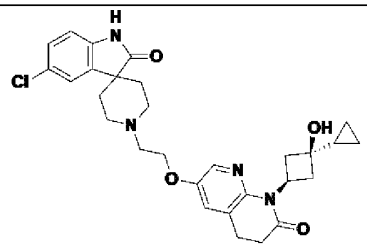
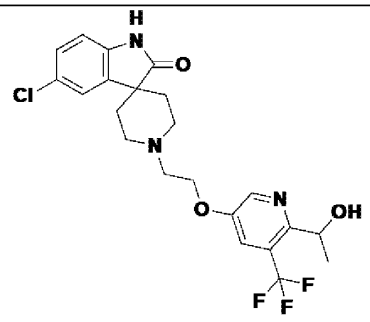
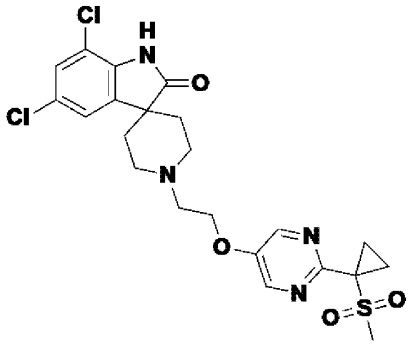
377		1'-[2-({6-[(1*R*) or (1*S*) -1-hydroxyethyl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
378		5-chloro-1'-[2-({2-[(1*S*) or (1*R*) -1,2-dihydroxyethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
379		5-chloro-1'-[2-({2-[(1*R*) or (1*S*) -1,2-dihydroxyethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
380		5-chloro-1'-[2-({2-[(2*S*) or (2*R*)-1,2-dihydroxypropan-2-yl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

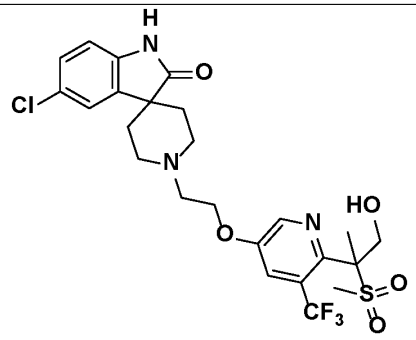
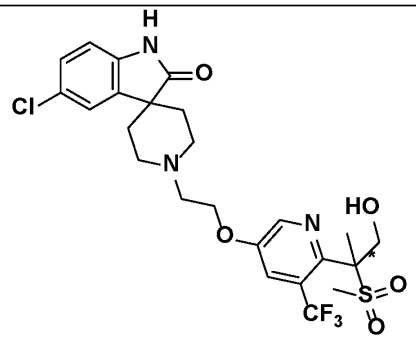
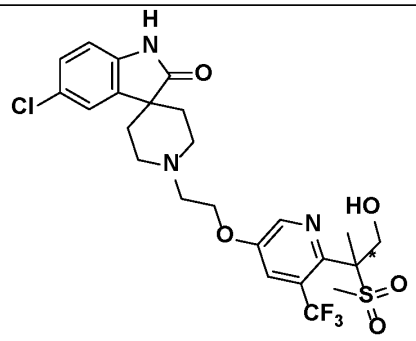
381		5-chloro-1'-[2-({2-[(2*R*) or (2*S*)-1,2-dihydroxypropan-2-yl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
382		5-chloro-1'-[2-({6-[(1*S*) or (1*R*)-1,2-dihydroxyethyl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
383		5-chloro-1'-[2-({6-[(1*R*) or (1*S*)-1,2-dihydroxyethyl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
384		5-chloro-1'-[2-({6-[(2*S*) or (2*R*)-1,2-dihydroxypropan-2-yl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

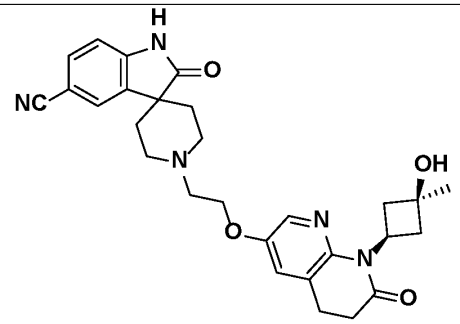
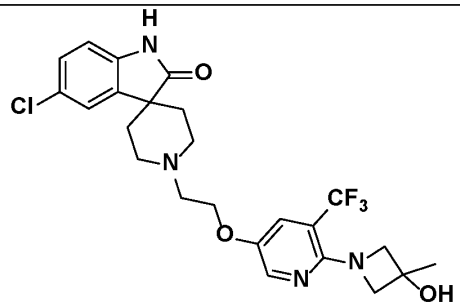
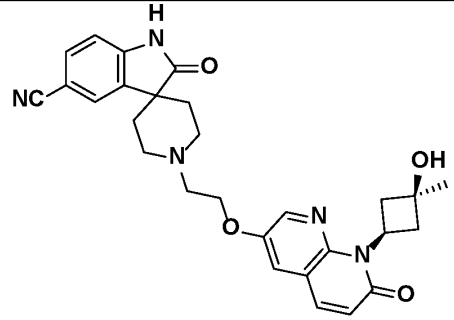
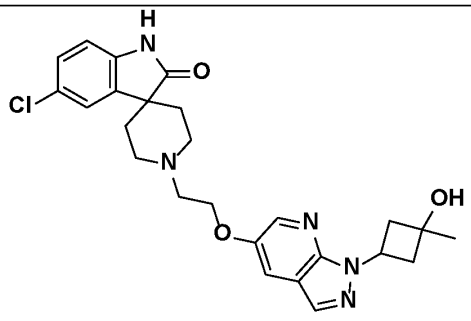
385		5-chloro-1'-[2-({6-[(2*R*) or (2*S*)-1,2-dihydroxypropan-2-yl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
386		5-chloro-1'-[2-({8-[(*cis*) or (*trans*)-3-hydroxy-3-methylcyclobutyl]-1,7-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
387		5-chloro-1'-[2-({8-[(*trans*) or (*cis*)-3-hydroxy-3-methylcyclobutyl]-1,7-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
388		5-chloro-1'-[2-({4-[(*cis*) or (*trans*)-3-hydroxy-3-methylcyclobutyl]pyrido[3,2-d]pyrimidin-7-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

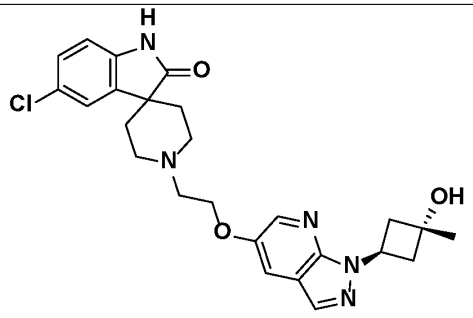
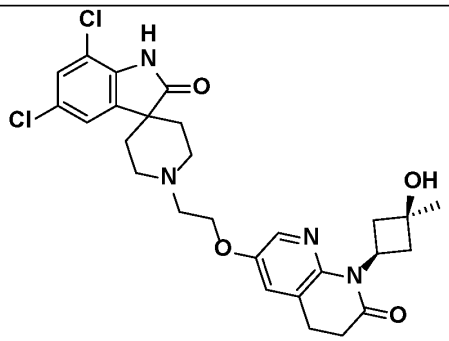
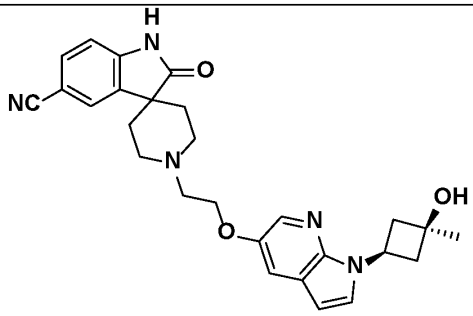
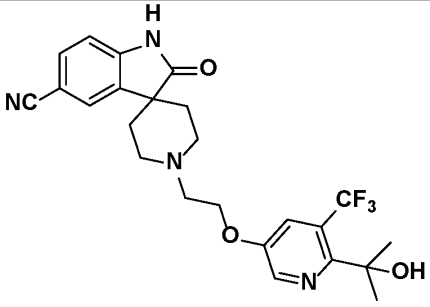
389		5-chloro-1'-[2-({4-[(*trans*) or (*cis*)-3-hydroxy-3-methylcyclobutyl]pyrido[3,2-d]pyrimidin-7-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
390		5-chloro-1'-[2-({8-[(*cis*) or (*trans*)-3-hydroxy-3-methylcyclobutyl]pyrido[2,3-d]pyridazin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
391		5-chloro-1'-[2-({8-[(*trans*) or *(cis*)-3-hydroxy-3-methylcyclobutyl]pyrido[2,3-d]pyridazin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
392		5-chloro-1'-[2-({2-[(*cis*) or (*trans*)-3-hydroxy-3-methylcyclobutyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

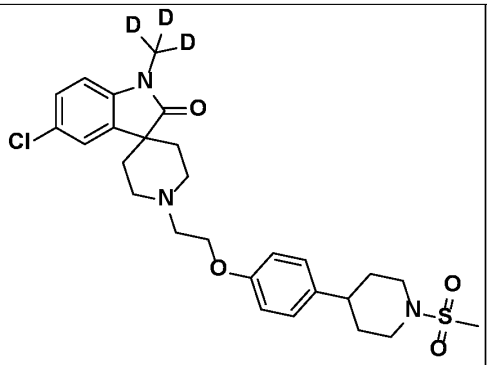
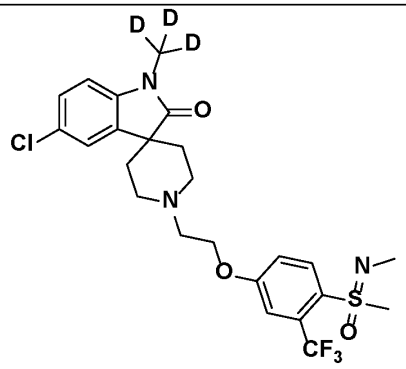
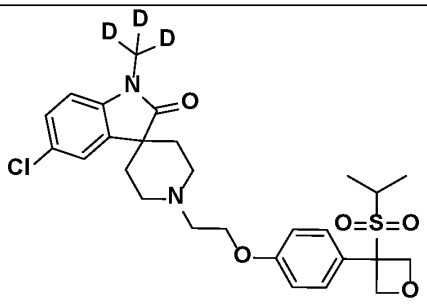
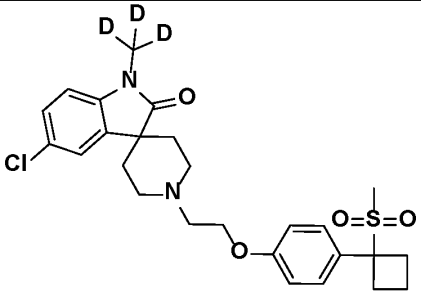
393		5-chloro-1'-[2-({2-[(*trans*) or (*cis*)-3-hydroxy-3-methylcyclobutyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
394		5-chloro-1'-[2-({2-oxo-3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-2H,3H-[1,3]oxazolo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
395		5-(difluoromethyl)-1'-(2-{[2-(3-hydroxy-3-methylazetidin-1-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
396		5-chloro-1'-{2-[(2-{6-hydroxy-2-azaspiro[3.3]heptan-2-yl}pyrimidin-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

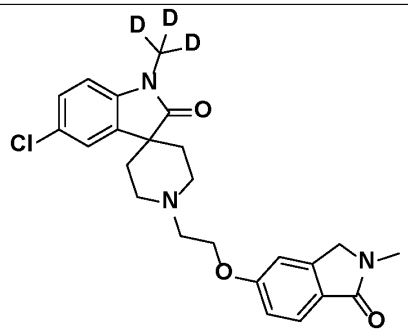
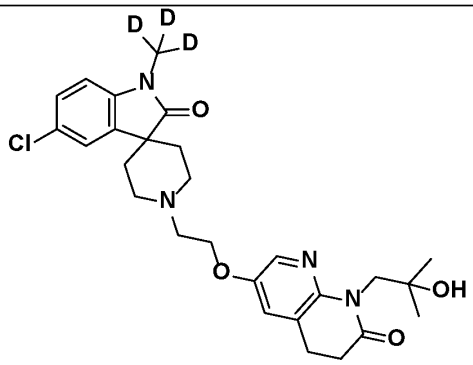
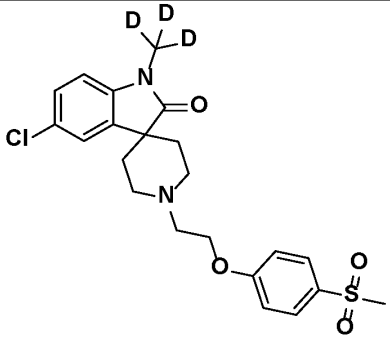
397		5-chloro-1'-(2-{[2-(3-ethyl-3-hydroxyazetidin-1-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
398		5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-cyclopropyl-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
399		5-chloro-1'-(2-{[6-(1-hydroxyethyl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
400		5,7-dichloro-1'-(2-{[2-(1-methanesulfonylcyclopropyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

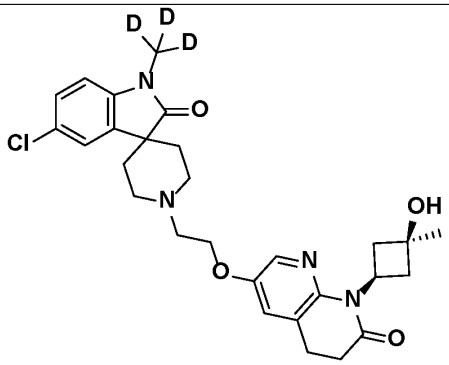
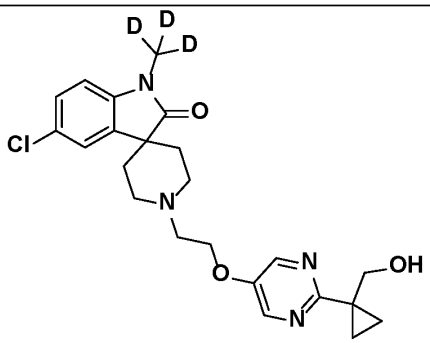
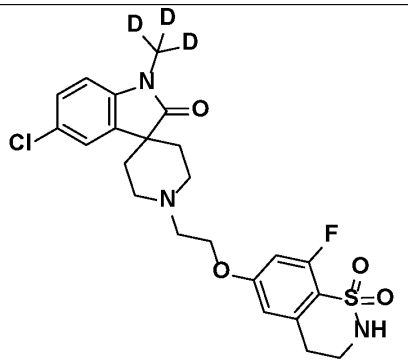
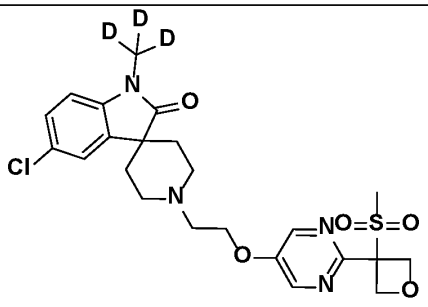
401		5-chloro-1'-(2-{[6-(1-hydroxy-2-methanesulfonylpropan-2-yl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
402		5-chloro-1'-[2-({6-[(2*S* or 2*R*)-1-hydroxy-2-methanesulfonylpropan-2-yl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
403		5-chloro-1'-[2-({6-[(2*R* or 2*S*)-1-hydroxy-2-methanesulfonylpropan-2-yl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

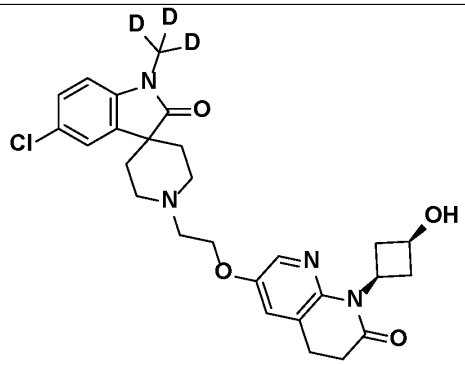
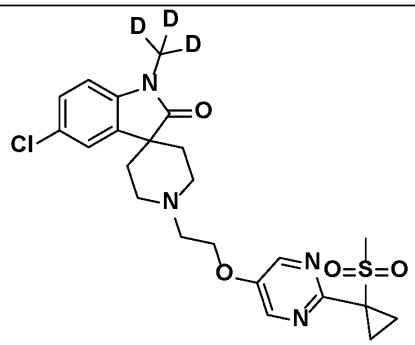
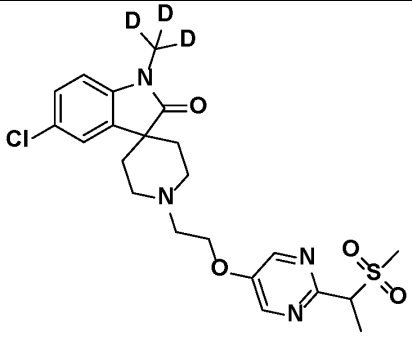
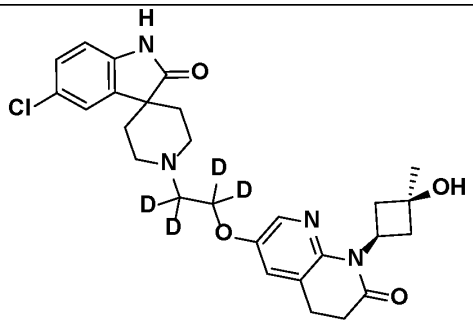
404		2-oxo-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
405		5-chloro-1'-(2-{[6-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
406		2-oxo-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
407		5-chloro-1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-1H-pyrazolo[3,4-b]pyridin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

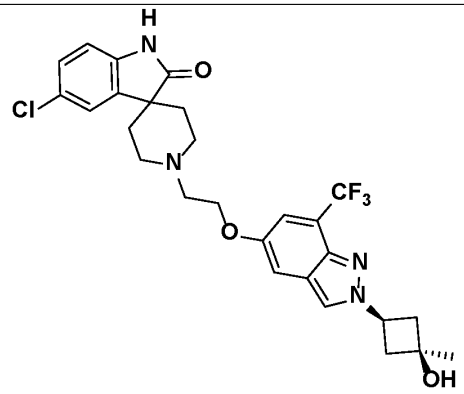
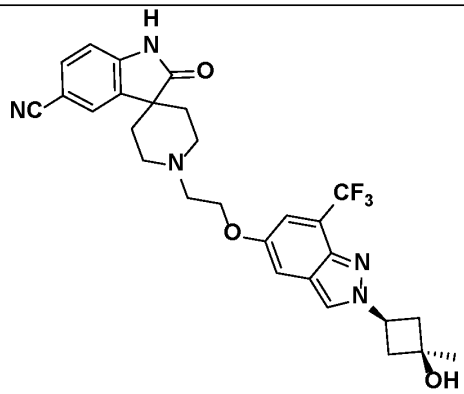
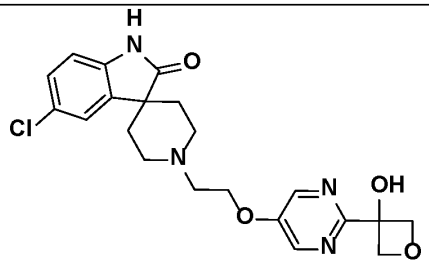
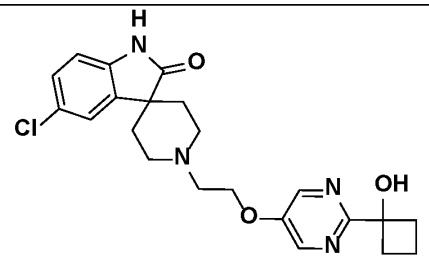
408		5-chloro-1'-[2-({1-[(*trans*)-3-hydroxy-3-methylcyclobutyl]-1H-pyrazolo[3,4-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
409		5,7-dichloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
410		2-oxo-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
411		1'-(2-{[6-(2-hydroxypropan-2-yl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile

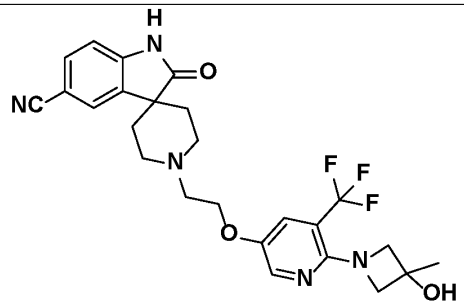
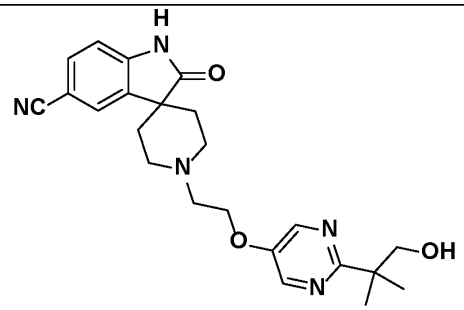
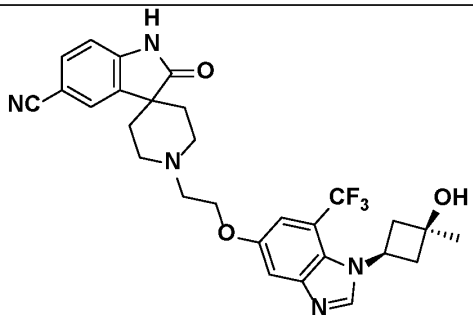
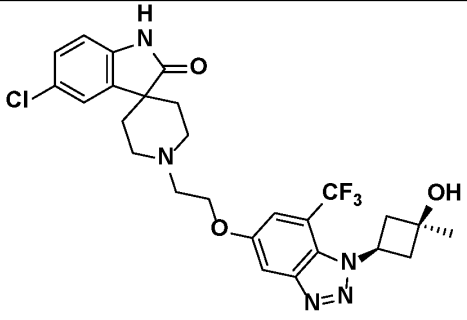
412		5-chloro-1'-{2-[4-(1-methanesulfonylpiperidin-4-yl)phenoxy]ethyl}-1-($^{2}H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
413		5-chloro-1-($^{2}H_3$)methyl-1'-(2-{4-[methyl(methylimino)oxo-λ^6-sulfanyl]-3-(trifluoromethyl)phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
414		5-chloro-1-($^{2}H_3$)methyl-1'-(2-{4-[3-(propane-2-sulfonyl)oxetan-3-yl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
415		5-chloro-1'-{2-[4-(1-methanesulfonylcyclobutyl)phenoxy]ethyl}-1-($^{2}H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

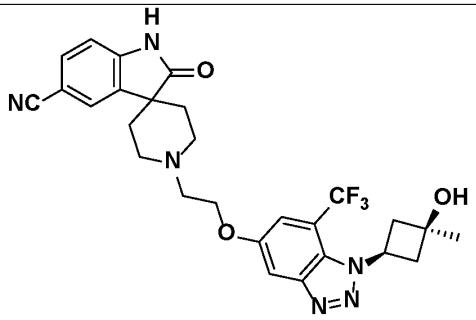
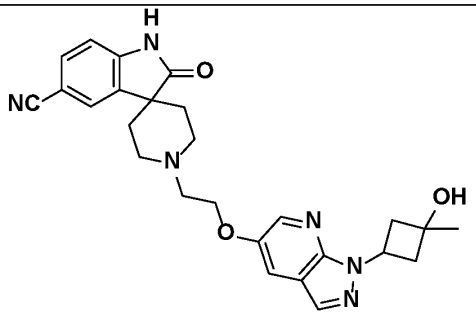
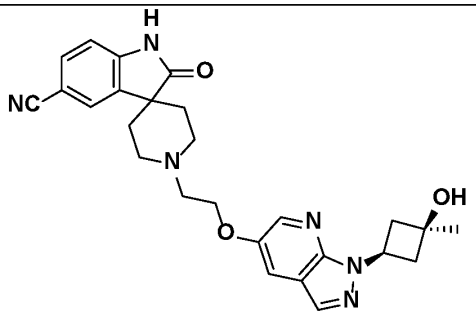
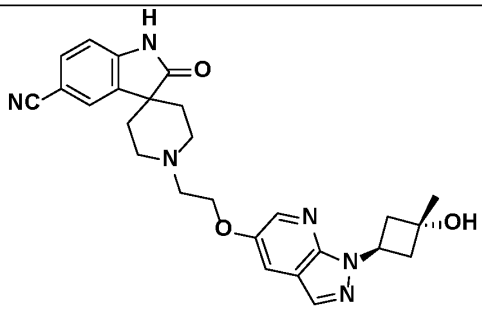
416		5-chloro-1-($^2H_3$)methyl-1'-{2-[(2-methyl-1-oxo-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
417		5-chloro-1'-(2-{[8-(2-hydroxy-2-methylpropyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1-($^2H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
418		5-chloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1-($^2H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

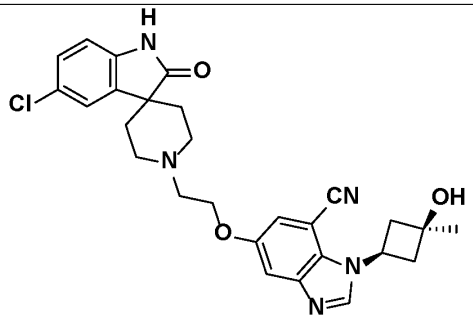
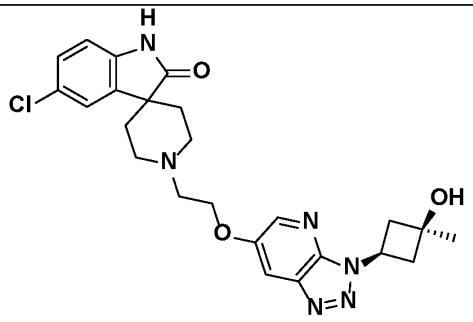
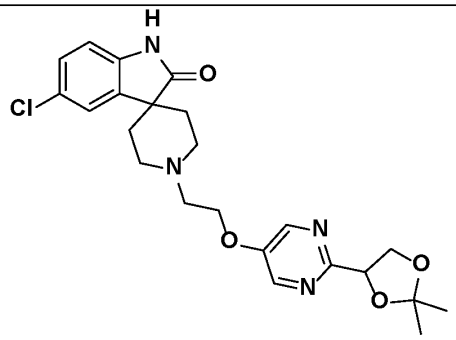
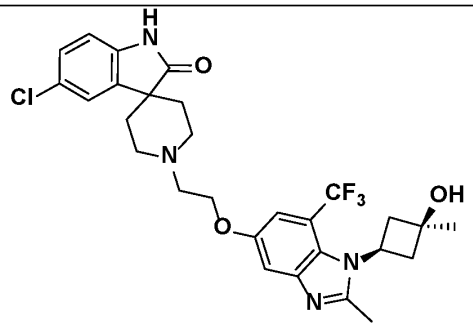
419		5-chloro-1-($^{2}H_3$)methyl-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
420		5-chloro-1'-[2-({2-[1-(hydroxymethyl)cyclopropyl]pyrimidin-5-yl}oxy)ethyl]-1-($^{2}H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
421		6-{2-[5-chloro-1-($^{2}H_3$)methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl]ethoxy}-8-fluoro-3,4-dihydro-2H-1λ^{6},2-benzothiazine-1,1-dione
422		5-chloro-1'-(2-{[2-(3-methanesulfonyloxetan-3-yl)pyrimidin-5-yl]oxy}ethyl)-1-($^{2}H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

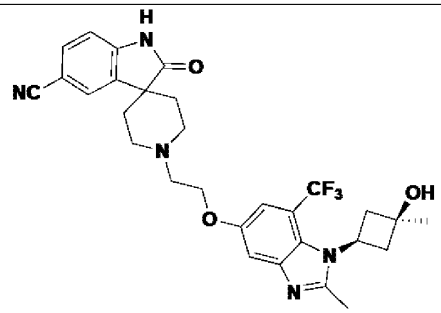
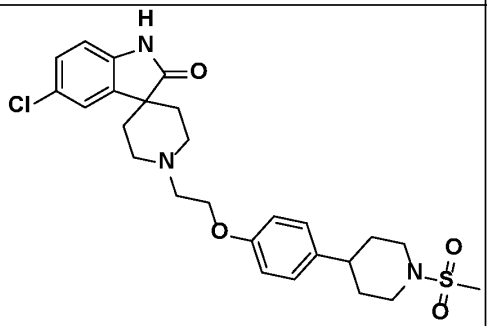
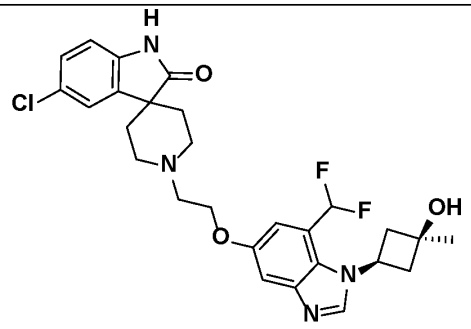
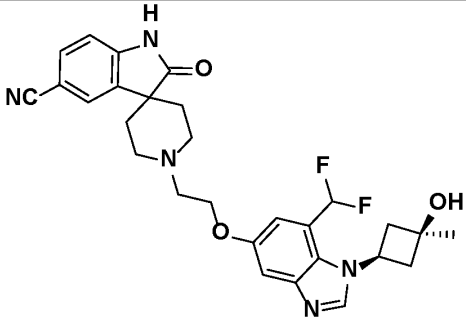
423		5-chloro-1-($^{2}H_3$)methyl-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
424		5-chloro-1'-(2-{[2-(1-methanesulfonylcyclopropyl)pyrimidin-5-yl]oxy}ethyl)-1-($^{2}H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
425		5-chloro-1'-(2-{[2-(1-methanesulfonylethyl)pyrimidin-5-yl]oxy}ethyl)-1-($^{2}H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
426		5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)(1,1,2,2-$^{2}H_4$)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

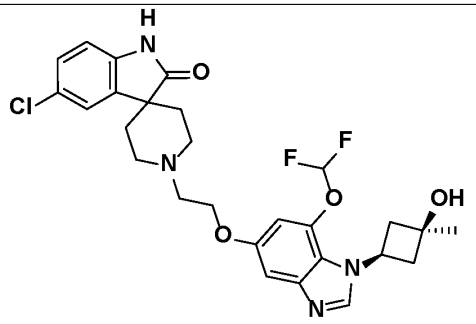
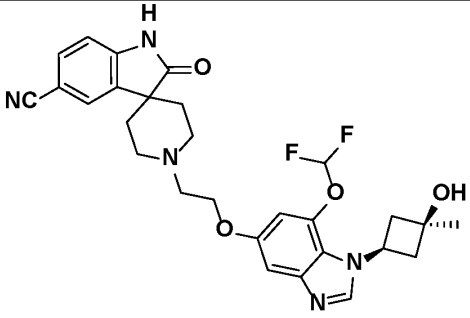
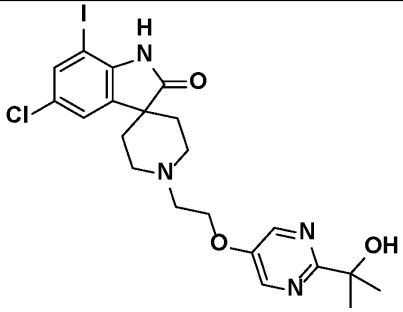
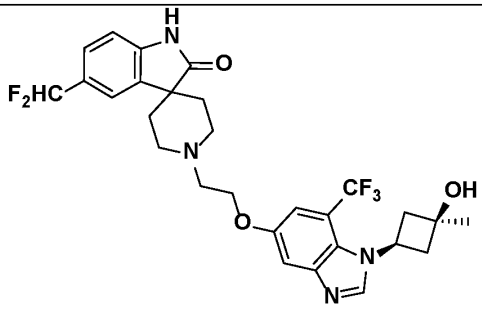
427		5-chloro-1'-[2-({2-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2H-indazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
428		2-oxo-1'-[2-({2-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2H-indazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
429		5-chloro-1'-(2-{[2-(3-hydroxyoxetan-3-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
430		5-chloro-1'-(2-{[2-(1-hydroxycyclobutyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

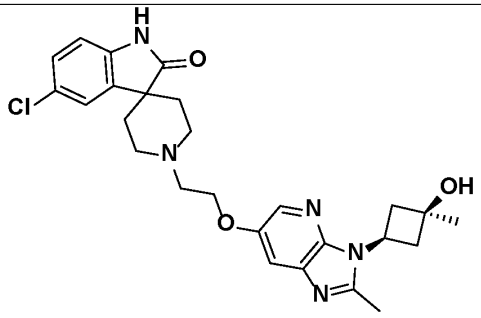
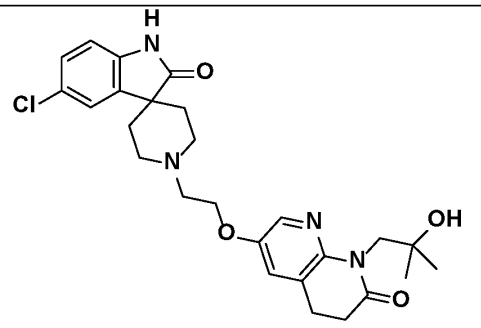
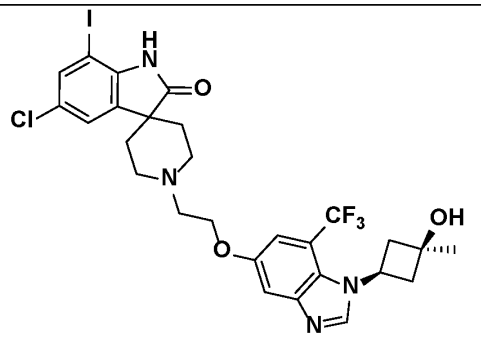
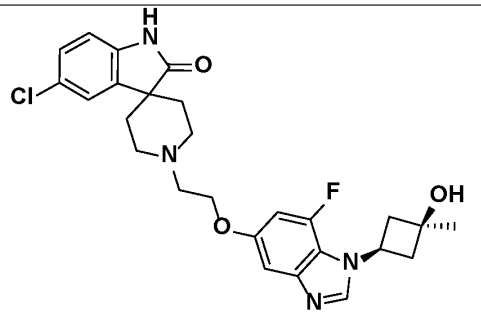
431		1'-(2-{[6-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
432		1'-(2-{[2-(1-hydroxy-2-methylpropan-2-yl)pyrimidin-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
433		2-oxo-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
434		5-chloro-1'-[2-({1-*[(cis)*-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,2,3-benzotriazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

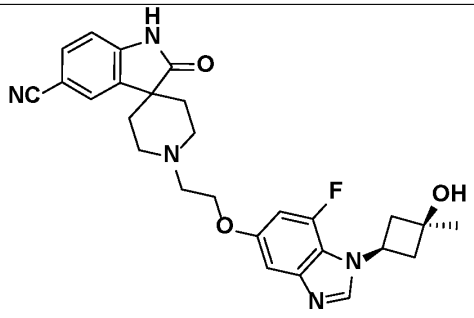
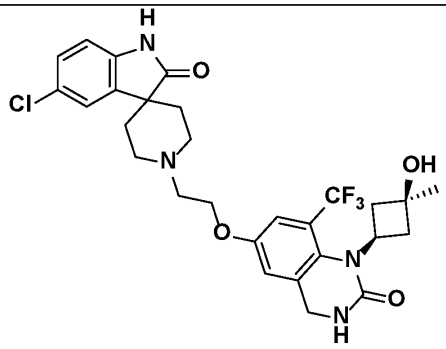
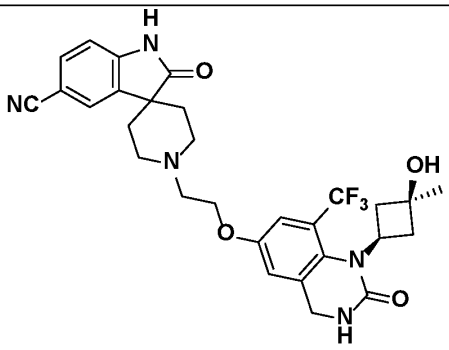
435		2-oxo-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,2,3-benzotriazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
436		1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-1H-pyrazolo[3,4-b]pyridin-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
437		2-oxo-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-pyrazolo[3,4-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
438		1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-1H-pyrazolo[3,4-b]pyridin-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile

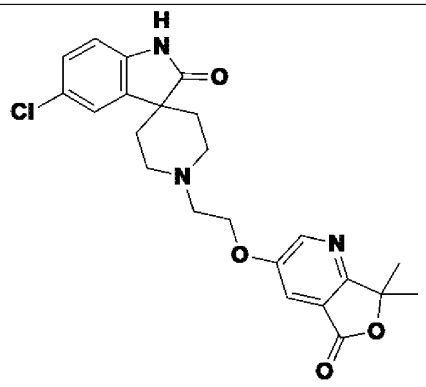
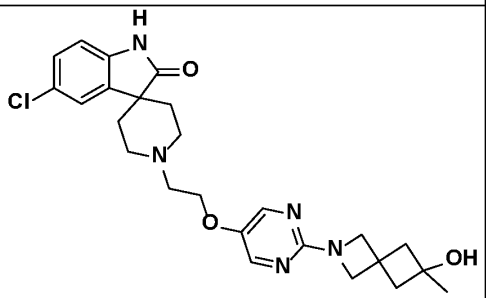
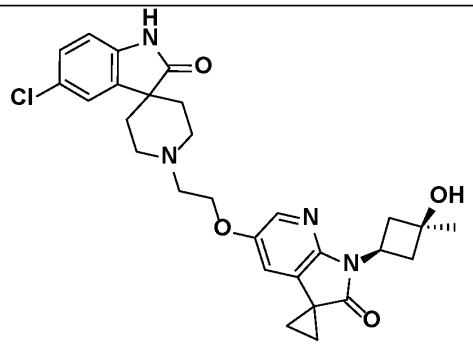
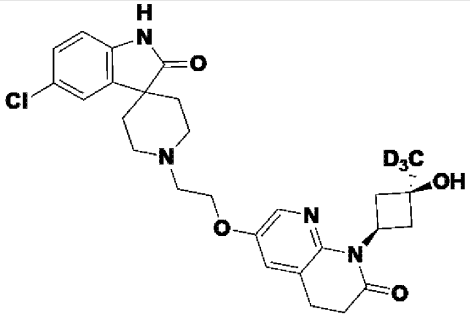
439		5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazole-7-carbonitrile
440		5-chloro-1'-[2-({3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-3H-[1,2,3]triazolo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
441		5-chloro-1'-(2-{[2-(2,2-dimethyl-1,3-dioxolan-4-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
442		5-chloro-1'-[2-({2-methyl-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

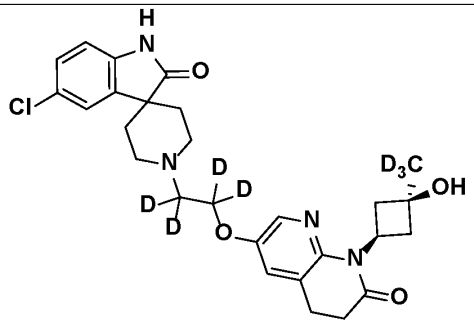
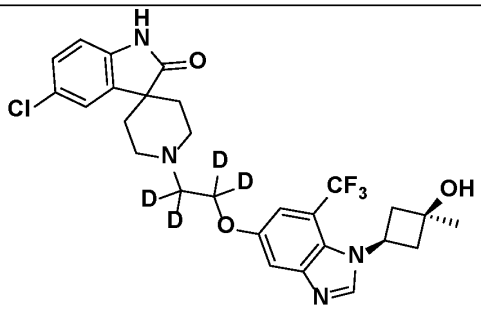
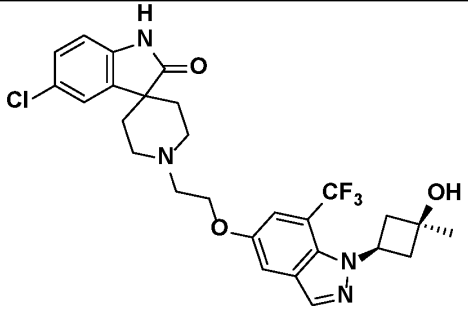
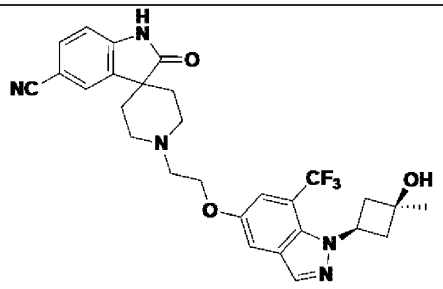
443		1'-[2-({2-methyl-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
444		5-chloro-1'-{2-[4-(1-methanesulfonylpiperidin-4-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
445		5-chloro-1'-(2-{[7-(difluoromethyl)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
446		1'-(2-{[7-(difluoromethyl)-1-*[(cis)*-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile

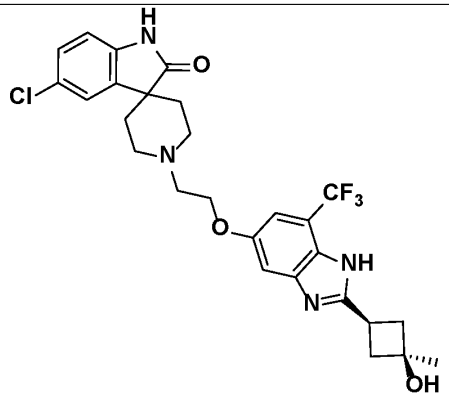
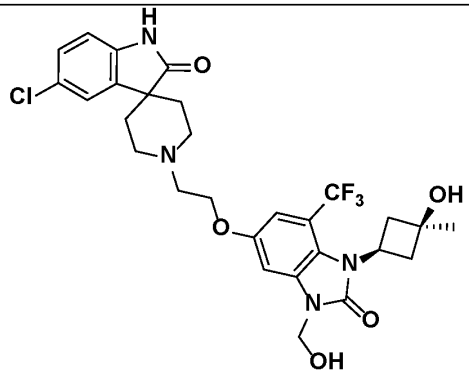
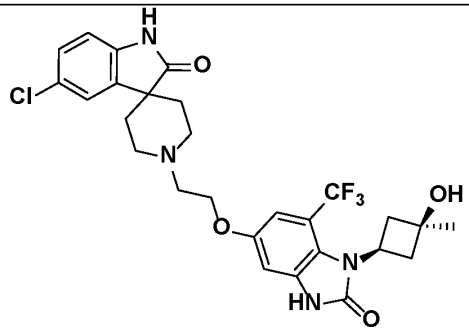
447		5-chloro-1'-(2-{[7-(difluoromethoxy)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
448		1'-(2-{[7-(difluoromethoxy)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
449		5-chloro-1'-(2-{[2-(2-hydroxypropan-2-yl)pyrimidin-5-yl]oxy}ethyl)-7-iodo-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
450		5-(difluoromethyl)-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

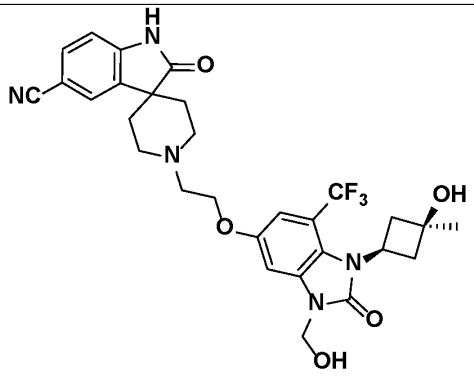
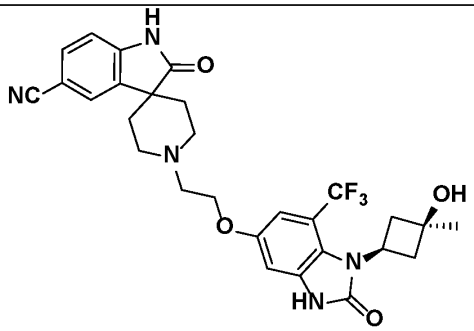
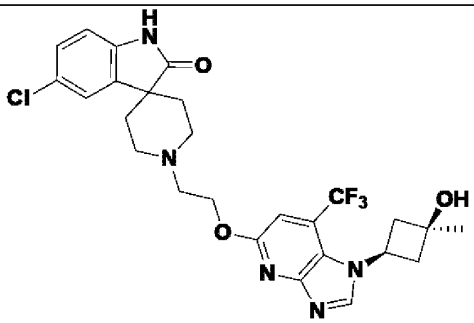
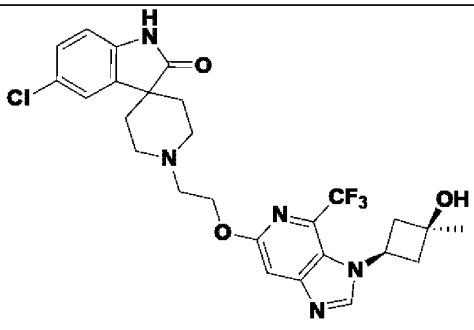
451		5-chloro-1'-[2-({2-methyl-3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-3H-imidazo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
452		5-chloro-1'-(2-{[8-(2-hydroxy-2-methylpropyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
453		5-chloro-7-iodo-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
454		5-chloro-1'-[2-({7-fluoro-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

455		1'-[2-({7-fluoro-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
456		5-chloro-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinazolin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
457		2-oxo-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinazolin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile

458		5-chloro-1'-[2-({7,7-dimethyl-5-oxo-5H,7H-furo[3,4-b]pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
459		5-chloro-1'-{2-[(2-{6-hydroxy-6-methyl-2-azaspiro[3.3]heptan-2-yl}pyrimidin-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
460		5-chloro-1'-(2-{2'-oxo-1'-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-5'-yloxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
461		5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-($^{2}H_3$)methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

462		5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-($^2H_3$)methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)(1,1,2,2-$^2H_4$)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
463		5-chloro-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)(1,1,2,2-$^2H_4$)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
464		5-chloro-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-indazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
465		2-oxo-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-indazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile

466		5-chloro-1'-[2-({2-[(1r,3s)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
467		5-chloro-1'-(2-{[3-(hydroxymethyl)-2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2,3-dihydro-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
468		5-chloro-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2,3-dihydro-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

469		1'-(2-{[3-(hydroxymethyl)-2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2,3-dihydro-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
470		2-oxo-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2,3-dihydro-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile
471		5-chloro-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-imidazo[4,5-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
472		5-chloro-1'-(2-{3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-4-(trifluoromethyl)-3H-1,3,5-triazainden-6-yloxy}ethyl)spiro[indoline-3,4'-piperidin]-2-one

[0452] In some embodiments, a compound of formula (I) is selected from the group consisting of:

1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-(4-methanesulfonylphenoxy)ethyl]-1-(2-methoxyethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-bromo-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-(4-methanesulfonylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{2-[(1-methyl-1H-indazol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-bromo-1-(2-hydroxyethyl)-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1-(2-methoxyethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-(4-methanesulfonylphenoxy)ethyl]-1-(2-methoxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{2-[(2-methanesulfonyl-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy]ethyl}-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[(2-acetyl-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy]ethyl}-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[1-(4-methanesulfonylphenoxy)propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1-[2-(4-methanesulfonylphenoxy)ethyl]-1',2'-dihydrospiro[azepane-4,3'-indol]-2'-one;
1'-[1-(4-methanesulfonylphenoxy)propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-(4-methanesulfonylphenoxy)propyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(1-methyl-1H-indazol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-(4-difluoromethanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-(3,5-difluoro-4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1-(3-hydroxycyclobutyl)-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-chloro-1'-{2-[4-(3-methanesulfonylpropanesulfonyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[4-(cyclopropanesulfonyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5,7-dichloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1-methyl-1'-{2-[4-(2-oxopyrrolidin-1-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[(1-acetyl-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1-methyl-1'-{2-[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1-methyl-1'-[2-(quinoxalin-6-yloxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1-methyl-1'-{2-[(1-methyl-2-oxo-2,3-dihydro-1H-indol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(2-{1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,3-dihydro-1lambda6-benzothiophene-1,1-dione;
5-chloro-1-(2-hydroxyethyl)-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[4-(1-methanesulfonylethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1-(oxetan-3-yl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
7-chloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[4-(1-methanesulfonylethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[4-(1-methanesulfonylethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[1-(propan-2-yl)-1H-indazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-chloro-1'-(2-{[1-(3-methanesulfonylpropyl)-1H-indazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(6-methanesulfonylpyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(2-methanesulfonyl-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[1-(4-methanesulfonylphenoxy)propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-(4-methanesulfonylphenoxy)propyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[4-(3-methanesulfonylpropanesulfonyl)phenoxy]ethyl}-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1-methyl-1'-{2-[4-(1-methyl-1H-pyrazol-4-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1-methyl-1'-{2-[(2-methyl-1-oxo-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1-methyl-1'-{2-[(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-(3-fluoro-4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-(4-methanesulfonylphenoxy)ethyl]-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-7-carbonitrile;
5-chloro-1'-(2-{4-[(3-hydroxycyclobutyl)sulfonyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[1-(oxetan-3-yl)-1H-indazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[4-(2-hydroxyethanesulfonyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-chloro-1'-{1-[(1-methyl-1H-indazol-5-yl)oxy]propan-2-yl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-(4-methanesulfonylphenoxy)ethyl]-5-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-(quinoxalin-6-yloxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(1-methyl-2-oxo-2,3-dihydro-1H-indol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-(3,5-difluoro-4-methanesulfonylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[4-(3-methyl-1H-pyrazol-4-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-(3,5-difluoro-4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(1-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[3-(difluoromethyl)-4-methanesulfonylphenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(1-methanesulfonyl-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[(1-acetyl-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-(1H-indazol-5-yloxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-methyl-1,2,3,4-tetrahydroquinoline-1-carboxamide;
1'-{2-[(2-acetyl-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-(4-methanesulfonyl-3-methylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-(4-difluoromethanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

1'-[2-(4-difluoromethanesulfonylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
N-{2-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzenesulfonyl]ethyl}-N-methylacetamide;
5-chloro-1'-{2-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-(4-methanesulfonyl-3-methylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{2-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[(2-methanesulfonyl-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{4-[(3-methyloxetan-3-yl)sulfonyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-methyl-1,2,3,4-tetrahydroisoquinoline-2-carboxamide;
5-chloro-1'-(2-{[1-(3-hydroxycyclobutyl)-1H-indazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,3-dihydro-1lambda6-benzothiophene-1,1-dione;
1'-{2-[3-(difluoromethyl)-4-methanesulfonylphenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{2-[(2-acetyl-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy]ethyl}-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{4-[(3-hydroxycyclobutyl)sulfonyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[1-(3-hydroxycyclobutyl)-1H-indazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-methyl-2,3-dihydro-1H-isoindole-2-carboxamide;

1'-(2-{4-[(3-methyloxetan-3-yl)sulfonyl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-(2-fluoro-4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
2-oxo-1'-(2-{[2-oxo-1-(propan-2-yl)-1,2,3,4-tetrahydroquinolin-6-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{2-[4-(1-methanesulfonylcyclopropyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-(2-{[1-(2-hydroxyethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[2-oxo-1-(propan-2-yl)-1,2,3,4-tetrahydroquinolin-6-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{1-[3-(difluoromethyl)-4-methanesulfonylphenoxy]propan-2-yl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[4-(1-methanesulfonylcyclopropyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{1-[3-(difluoromethyl)-4-methanesulfonylphenoxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1-(3-hydroxycyclobutyl)-1'-[1-(4-methanesulfonylphenoxy)propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-chloro-1'-{1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
N-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-N-methylmethanesulfonamide;
N-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-N-methylmethanesulfonamide;
5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-methanesulfonylbenzonitrile;
5-chloro-1'-(2-{[1-(2,2-difluoroethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[4-methanesulfonyl-3-(trifluoromethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[4-methanesulfonyl-3-(trifluoromethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
methyl 1-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzenesulfonyl]cyclopropane-1-carboxylate;
1'-{2-[3-(difluoromethyl)-4-methanesulfonylphenoxy]ethyl}-1-(2-hydroxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[3-(difluoromethyl)-4-methanesulfonylphenoxy]ethyl}-1-(2-hydroxyethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-(2-{[1-(2,2-difluoroethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1-(3-hydroxycyclobutyl)-1'-[1-(4-methanesulfonylphenoxy)propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
2-oxo-1'-{2-[(1,3,3-trimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzamide;
4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzamide;
5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)pyridine-2-carboxamide;

6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-1-methyl-3,4-dihydro-1H-2lambda6,1-benzothiazine-2,2-dione;
N-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]methanesulfonamide;
1'-{2-[(1-methyl-2,2-dioxo-3,4-dihydro-1H-2lambda6,1-benzothiazin-6-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-(2-{[1-(oxetan-3-yl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1-(3-hydroxycyclobutyl)-1'-[1-(4-methanesulfonylphenoxy)propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1-(3-hydroxycyclobutyl)-1'-[1-(4-methanesulfonylphenoxy)propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1-(3-hydroxycyclobutyl)-1'-[1-(4-methanesulfonylphenoxy)propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-(4-{[1-(hydroxymethyl)cyclopropyl]sulfonyl}phenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-(3-fluoro-4-methanesulfonylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{2-[(1-acetyl-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[(8-methyl-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[(8-methyl-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-[2-(4-methanesulfonyl-3,5-dimethylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

2-oxo-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
6-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-methyl-1,2,3,4-tetrahydroisoquinoline-2-carboxamide;
5-chloro-1'-(2-{[1-(3-hydroxycyclobutyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-(4-methanesulfonyl-3,5-dimethylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
2-oxo-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
2-oxo-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{2-[4-(1-methanesulfonylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[4-(1-cyano-1-methylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
2-oxo-1'-(2-{[2-oxo-1-(propan-2-yl)-2,3-dihydro-1H-indol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[(6-methanesulfonyl-5-methylpyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[4-(1-methanesulfonylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;

1'-{2-[4-(1-methanesulfonylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-({3-methyl-2-oxo-1H,2H,3H-imidazo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[(6-methanesulfonyl-5-methylpyridin-3-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-(2-{4-[methyl(methylimino)oxo-lambda6-sulfanyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-(2-{4-[methyl(methylimino)oxo-lambda6-sulfanyl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{2-[(8-acetyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[(8-acetyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[4-methanesulfonyl-3-(oxetan-3-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[3,5-difluoro-4-(1-methanesulfonylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-(3-chloro-4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-(3-chloro-4-methanesulfonylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-(2-{[2-oxo-1-(propan-2-yl)-2,3-dihydro-1H-indol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(2-methyl-1-oxo-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
2-oxo-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;

1'-[1-(3,5-difluoro-4-methanesulfonylphenoxy)propan-2-yl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
2-oxo-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
2-oxo-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-methylbenzamide;
5-chloro-1'-{2-[(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluoro-N,N-dimethylbenzamide;
5-chloro-1'-{2-[3-fluoro-4-(morpholine-4-carbonyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
4-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzoyl]-1lambda6-thiomorpholine-1,1-dione;
1'-[2-(4-{[1-(azetidine-1-carbonyl)cyclopropyl]sulfonyl}phenoxy)ethyl]-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[3-fluoro-4-(3-methanesulfonylazetidine-1-carbonyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-methyl-3,4-dihydro-2H-1lambda6,2-benzothiazine-1,1-dione;
1'-{2-[(2-methyl-1,1-dioxo-3,4-dihydro-2H-1lambda6,2-benzothiazin-6-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{2-[4-(azetidine-1-carbonyl)-3-fluorophenoxy]ethyl}-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-chloro-1'-{2-[3,5-difluoro-4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[3-fluoro-4-(3-hydroxyazetidine-1-carbonyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[3,5-difluoro-4-(1-methanesulfonylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{2-[3,5-difluoro-4-(1-methanesulfonylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
N-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,6-difluorophenyl]-N-methylmethanesulfonamide;
4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluoro-N-methylbenzamide;
1-(2-hydroxyethyl)-1'-{2-[4-methanesulfonyl-3-(trifluoromethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
N-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,6-difluorophenyl]-N-methylmethanesulfonamide;
1-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzenesulfonyl]-N-methylcyclopropane-1-carboxamide;
5-chloro-1'-{2-[3-(1,2-difluoroethyl)-4-methanesulfonylphenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzenesulfonyl]-N,N-dimethylcyclopropane-1-carboxamide;
1'-{2-[3,5-difluoro-4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[3-(1,2-dihydroxyethyl)-4-methanesulfonylphenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N,N-dimethylpyridine-2-carboxamide;
4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzamide;

1'-{2-[4-(3-aminoazetidine-1-carbonyl)-3-fluorophenoxy]ethyl}-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({6-[(3-methyloxetan-3-yl)sulfonyl]pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[3,5-difluoro-4-(1-methanesulfonylethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[3,5-difluoro-4-(1-methanesulfonylethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[3,5-difluoro-4-(1-methanesulfonylethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[3-(1,2-difluoroethyl)-4-methanesulfonylphenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[1-(3-hydroxycyclobutyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[3-(1,2-difluoroethyl)-4-methanesulfonylphenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
N-{1-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzoyl]azetidin-3-yl}methanesulfonamide;
1'-{2-[3-(1,2-difluoroethyl)-4-methanesulfonylphenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-methylbenzamide;
1'-(2-{4-[methyl(methylimino)oxo-lambda6-sulfanyl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{1-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-(2-{4-[methyl(methylimino)oxo-lambda6-sulfanyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1-(2-hydroxyethyl)-1'-{2-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-chloro-1'-(2-{4-[methyl(methylimino)oxo-lambda6-sulfanyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-(2-{4-[methyl(methylimino)oxo-lambda6-sulfanyl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-[2-(4-{[dimethyl(oxo)-lambda6-sulfanylidene]amino}phenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{2-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-2-oxo-1-(2,2,2-trifluoroethyl)-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-1-(2,2,2-trifluoroethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[4-(1-methanesulfonylcyclobutyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{2-[3-(difluoromethoxy)-4-methanesulfonylphenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[3-(difluoromethoxy)-4-methanesulfonylphenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(6-{[1-(hydroxymethyl)cyclopropyl]sulfonyl}pyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{1-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{2-[3-(1,2-difluoroethyl)-4-methanesulfonylphenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{1-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[4-(1-methanesulfonylcyclobutyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[(7-fluoro-1-methyl-2-oxo-2,3-dihydro-1H-indol-5-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{2-[3-(1,2-difluoroethyl)-4-methanesulfonylphenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;

1'-{2-[4-(4-methanesulfonyloxan-4-yl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[4-(4-methanesulfonyloxan-4-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-(2-{3-oxo-3H-spiro[2-benzofuran-1,3'-oxetan]-5-yloxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[4-(3-methanesulfonyloxetan-3-yl)-3-(trifluoromethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
N-(4-{2-[5-chloro-1-(2-hydroxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl]ethoxy}-2-(trifluoromethyl)phenyl)methanesulfonamide;
1'-{2-[4-(3-methanesulfonyloxetan-3-yl)-3-(trifluoromethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-3,4-dihydro-2H-1lambda6,2-benzothiazine-1,1-dione;
2-oxo-1'-{2-[(1-oxo-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[(1-oxo-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(7-fluoro-2-oxo-2,3-dihydro-1H-indol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[(1,1-dioxo-3,4-dihydro-2H-1lambda6,2-benzothiazin-6-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-({2-[(3-methyloxetan-3-yl)oxy]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
3-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-N-methyloxetane-3-carboxamide;
3-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-N,N-dimethyloxetane-3-carboxamide;

2-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-1lambda6-thiolane-1,1-dione;
2-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-1lambda6-thiolane-1,1-dione;
1'-[2-(4-{6-methanesulfonyl-2-oxaspiro[3.3]heptan-6-yl}phenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-(2-{4-[3-(azetidine-1-carbonyl)oxetan-3-yl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)pyrimidine-2-carboxamide;
2-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-1lambda6-thiolane-1,1-dione;
1'-(2-{4-[3-(ethanesulfonyl)oxetan-3-yl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
2-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-2-methylpropanamide;
1'-{2-[4-(1,1-dioxo-1lambda6-thiolan-2-yl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(difluoromethyl)benzamide;
1'-{2-[3,5-difluoro-4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-[2-({2-[(3-methyloxetan-3-yl)oxy]pyrimidin-5-yl}oxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-(2-{4-[3-(3-fluoroazetidine-1-carbonyl)oxetan-3-yl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(difluoromethyl)benzamide;
5-chloro-1'-[2-(4-{6-methanesulfonyl-2-oxaspiro[3.3]heptan-6-yl}phenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-chloro-1'-(2-{[2-(1-methanesulfonylethyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
N-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-N-(2-hydroxyethyl)methanesulfonamide;
6-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzoyl]-2lambda6-thia-6-azaspiro[3.3]heptane-2,2-dione;
5-chloro-1'-[2-(3-fluoro-4-{6-methanesulfonyl-2,6-diazaspiro[3.3]heptane-2-carbonyl}phenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
4-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,6-difluorobenzoyl]-1lambda6-thiomorpholine-1,1-dione;
5-chloro-1'-(2-{[8-(2-hydroxyethyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[2-(1-methanesulfonylcyclopropyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[4-(1,1-dioxo-1lambda6-thiomorpholine-4-carbonyl)-3,5-difluorophenoxy]ethyl}-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
4-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(trifluoromethyl)benzoyl]-1lambda6-thiomorpholine-1,1-dione;
1'-{2-[4-(1,1-dioxo-1lambda6-thiomorpholine-4-carbonyl)-3-(trifluoromethyl)phenoxy]ethyl}-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-(2-{[6-(2-methanesulfonylpropan-2-yl)pyridin-3-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-(2-{[2-(1-methanesulfonylcyclopropyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[8-(3-hydroxycyclobutyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
4-(4-{2-[5-chloro-1-(2-hydroxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl]ethoxy}-2-(trifluoromethyl)benzoyl)-1lambda6-thiomorpholine-1,1-dione;

4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-(1,1-dioxo-1lambda6-thiolan-3-yl)-2-fluorobenzamide;
5-chloro-1'-{2-[4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-(1,1-dioxo-1lambda6-thian-4-yl)-2-fluorobenzamide;
4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-(1,1-dioxo-1lambda6-thiolan-3-yl)-2-fluorobenzamide;
4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-(1,1-dioxo-1lambda6-thiolan-3-yl)-2-fluorobenzamide;
5-chloro-1'-(2-{[8-(3-hydroxycyclobutyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethoxy)-1'-(2-{[2-(1-methanesulfonylcyclopropyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[2-(1-methanesulfonylethyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[2-(1-methanesulfonylethyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-[2-({7-oxo-8-[3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({7-oxo-8-[3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-oxo-1-[3-hydroxy-3-methylcyclobutyl]-1H,2H,4H-pyrido[2,3-d][1,3]oxazin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({7-oxo-8-[3-ethyl-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-chloro-1'-[2-({7-oxo-8-[3-cyclopropyl-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[8-(3-cyclopropyl-3-hydroxycyclobutyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[8-(3-hydroxy-3-methylazetidin-1-yl)-1,7-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({7-oxo-8-[3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-[2-({7-oxo-8-[3-(hydroxymethyl)cyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-{2-[(7-oxo-8-{[3-hydroxy-3-methylcyclobutyl]methyl}-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(7-oxo-8-{[3-hydroxy-3-methylcyclobutyl]methyl}-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[8-(3-hydroxyazetidin-1-yl)-1,7-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[8-(3-hydroxy-3-methylcyclobutyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-[2-({8-[3-(hydroxymethyl)cyclobutyl]-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one ;
5-chloro-1'-[2-({7-oxo-8-[3-hydroxy-3-(propan-2-yl)cyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[8-(3-ethyl-3-hydroxycyclobutyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({7-oxo-8-[3-(hydroxymethyl)cyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one ;
5-(difluoromethyl)-1'-[2-({8-[(3-hydroxy-3-methylcyclobutyl)methyl]-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({7-oxo-8-[3-ethyl-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-chloro-1'-[2-({7-oxo-8-[3-hydroxy-3-methylcyclobutyl]-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-[2-({7-oxo-8-[3-hydroxy-3-methylcyclobutyl]-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethoxy)-1'-[2-({7-oxo-8-[3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({8-[3-(hydroxymethyl)cyclobutyl]-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({8-[(3-hydroxy-3-methylcyclobutyl)methyl]-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethoxy)-1'-[2-({7-oxo-8-[3-hydroxy-3-methylcyclobutyl]-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-7-iodo-1'-[2-({7-oxo-8-[3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({7-oxo-8-[3-hydroxy-3-(propan-2-yl)cyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({7-oxo-8-[3-(hydroxymethyl)cyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-(2-{[6-(1-hydroxyethyl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one ;
1'-(2-{[6-(1-hydroxyethyl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-(2-{[5-(difluoromethyl)-7-oxo-8-[(cis)-3-hydroxy-3-methylcyclobutyl]-7,8-dihydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-(2-{[5-(difluoromethyl)-7-oxo-8-[(cis)-3-hydroxy-3-methylcyclobutyl]-7,8-dihydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({7-oxo-8-[3-hydroxy-3-methylcyclobutyl]-5-(trifluoromethyl)-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-[2-({7-oxo-8-[3-hydroxy-3-methylcyclobutyl]-5-(trifluoromethyl)-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-chloro-1'-[2-({2-oxo-1-[3-hydroxy-3-methylcyclobutyl]-1H,2H,3H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-[2-({2-oxo-1-[3-hydroxy-3-methylcyclobutyl]-1H,2H,3H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-oxo-1-[3-hydroxy-3-methylcyclobutyl]-1H,2H,3H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-[2-({2-oxo-1-[3-hydroxy-3-methylcyclobutyl]-1H,2H,3H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one ;
5-chloro-1'-[2-({1-[3-hydroxy-3-methylcyclobutyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-[2-({1-[3-hydroxy-3-methylcyclobutyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-oxo-1-[3-hydroxy-3-methylcyclobutyl]-1H,2H-pyrido[2,3-d]pyrimidin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-oxo-1-[3-hydroxy-3-methylcyclobutyl]-1H,2H,3H,4H-pyrido[2,3-d]pyrimidin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({1-[3-hydroxy-3-methylcyclobutyl]-1H-pyrazolo[3,4-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({3-oxo-4-[3-hydroxy-3-methylcyclobutyl]-3H,4H-pyrido[2,3-b]pyrazin-7-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[4-(3-hydroxy-3-methylcyclobutyl)pyrido[3,2-d]pyrimidin-7-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[8-(3-hydroxy-3-methylcyclobutyl)-1,7-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[8-(3-hydroxy-3-methylazetidin-1-yl)pyrido[2,3-d]pyridazin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[4-(3-hydroxy-3-methylazetidin-1-yl)pyrido[3,2-d]pyrimidin-7-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[8-(3-hydroxyazetidin-1-yl)pyrido[2,3-d]pyridazin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-chloro-1'-(2-{[4-(3-hydroxyazetidin-1-yl)pyrido[3,2-d]pyrimidin-7-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({3-[3-hydroxy-3-methylcyclobutyl]-3H-imidazo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one ;
5-chloro-1'-[2-({2-oxo-3-[3-hydroxy-3-methylcyclobutyl]-1H,2H,3H-imidazo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({8-[3-(hydroxymethyl)azetidin-1-yl]-1,7-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-oxo-3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-2H,3H-[1,3]oxazolo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-(2-{[2-(3-hydroxy-3-methylazetidin-1-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(2-{6-hydroxy-2-azaspiro[3.3]heptan-2-yl}pyrimidin-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[2-(3-ethyl-3-hydroxyazetidin-1-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-cyclopropyl-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[6-(1-hydroxyethyl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5,7-dichloro-1'-(2-{[2-(1-methanesulfonylcyclopropyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[6-(1-hydroxy-2-methanesulfonylpropan-2-yl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[6-(1-hydroxy-2-methanesulfonylpropan-2-yl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[6-(1-hydroxy-2-methanesulfonylpropan-2-yl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-(2-{[8-(3-hydroxy-3-methylcyclobutyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;

5-chloro-1'-(2-{[6-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-(2-{[8-(3-hydroxy-3-methylcyclobutyl)-7-oxo-7,8-dihydro-1,8-naphthyridin-3-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-1H-pyrazolo[3,4-b]pyridin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-1H-pyrazolo[3,4-b]pyridin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5,7-dichloro-1'-(2-{[8-(3-hydroxy-3-methylcyclobutyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-(2-{[6-(2-hydroxypropan-2-yl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[4-(1-methanesulfonylpiperidin-4-yl)phenoxy]ethyl}-1-(2H3)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1-(2H3)methyl-1'-(2-{4-[methyl(methylimino)oxo-lambda6-sulfanyl]-3-(trifluoromethyl)phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1-(2H3)methyl-1'-(2-{4-[3-(propane-2-sulfonyl)oxetan-3-yl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[4-(1-methanesulfonylcyclobutyl)phenoxy]ethyl}-1-(2H3)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1-(2H3)methyl-1'-{2-[(2-methyl-1-oxo-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[8-(2-hydroxy-2-methylpropyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1-(2H3)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1-(2H3)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[8-(3-hydroxy-3-methylcyclobutyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1-(2H3)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-chloro-1'-[2-({2-[1-(hydroxymethyl)cyclopropyl]pyrimidin-5-yl}oxy)ethyl]-1-(2H3)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
6-{2-[5-chloro-1-(2H3)methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl]ethoxy}-8-fluoro-3,4-dihydro-2H-1lambda6,2-benzothiazine-1,1-dione;
5-chloro-1'-(2-{[2-(3-methanesulfonyloxetan-3-yl)pyrimidin-5-yl]oxy}ethyl)-1-(2H3)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[8-(3-hydroxycyclobutyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1-(2H3)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[2-(1-methanesulfonylcyclopropyl)pyrimidin-5-yl]oxy}ethyl)-1-(2H3)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[2-(1-methanesulfonylethyl)pyrimidin-5-yl]oxy}ethyl)-1-(2H3)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[8-(3-hydroxy-3-methylcyclobutyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}(1,1,2,2-2H4)ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[2-(3-hydroxy-3-methylcyclobutyl)-7-(trifluoromethyl)-2H-indazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-(2-{[2-(3-hydroxy-3-methylcyclobutyl)-7-(trifluoromethyl)-2H-indazol-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-(2-{[2-(3-hydroxyoxetan-3-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[2-(1-hydroxycyclobutyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-(2-{[6-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-(2-{[2-(1-hydroxy-2-methylpropan-2-yl)pyrimidin-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-7-(trifluoromethyl)-1H-1,2,3-benzotriazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-7-(trifluoromethyl)-1H-1,2,3-benzotriazol-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-1H-pyrazolo[3,4-b]pyridin-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-1H-pyrazolo[3,4-b]pyridin-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-1H-pyrazolo[3,4-b]pyridin-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-1-(3-hydroxy-3-methylcyclobutyl)-1H-1,3-benzodiazole-7-carbonitrile;
5-chloro-1'-(2-{[3-(3-hydroxy-3-methylcyclobutyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-6-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[2-(2,2-dimethyl-1,3-dioxolan-4-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-2-methyl-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-2-methyl-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[4-(1-methanesulfonylpiperidin-4-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[7-(difluoromethyl)-1-(3-hydroxy-3-methylcyclobutyl)-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-(2-{[7-(difluoromethyl)-1-(3-hydroxy-3-methylcyclobutyl)-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-(2-{[7-(difluoromethoxy)-1-(3-hydroxy-3-methylcyclobutyl)-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-(2-{[7-(difluoromethoxy)-1-(3-hydroxy-3-methylcyclobutyl)-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-(2-{[2-(2-hydroxypropan-2-yl)pyrimidin-5-yl]oxy}ethyl)-7-iodo-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-(difluoromethyl)-1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[3-(3-hydroxy-3-methylcyclobutyl)-2-methyl-3H-imidazo[4,5-b]pyridin-6-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[8-(2-hydroxy-2-methylpropyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-7-iodo-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[7-fluoro-1-(3-hydroxy-3-methylcyclobutyl)-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-(2-{[7-fluoro-1-(3-hydroxy-3-methylcyclobutyl)-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-2-oxo-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinazolin-6-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-2-oxo-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinazolin-6-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-({7,7-dimethyl-5-oxo-5H,7H-furo[3,4-b]pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(2-{6-hydroxy-6-methyl-2-azaspiro[3.3]heptan-2-yl}pyrimidin-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[1'-(3-hydroxy-3-methylcyclobutyl)-2'-oxo-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-5'-yloxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({8-[3-hydroxy-3-(2H3)methylcyclobutyl]-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({8-[3-hydroxy-3-(2H3)methylcyclobutyl]-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)(1,1,2,2-2H4)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl]oxy}(1,1,2,2-2H4)ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-7-(trifluoromethyl)-1H-indazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-7-(trifluoromethyl)-1H-indazol-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-(2-{[2-(3-hydroxy-3-methylcyclobutyl)-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-3-(hydroxymethyl)-2-oxo-7-(trifluoromethyl)-2,3-dihydro-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-2-oxo-7-(trifluoromethyl)-2,3-dihydro-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-3-(hydroxymethyl)-2-oxo-7-(trifluoromethyl)-2,3-dihydro-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-2-oxo-7-(trifluoromethyl)-2,3-dihydro-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-7-(trifluoromethyl)-1H-imidazo[4,5-b]pyridin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one; and
5-chloro-1'-(2-{3-[(3-hydroxy-3-methylcyclobutyl]-4-(trifluoromethyl)-3H-1,3,5-triazainden-6-yloxy}ethyl)spiro[indoline-3,4'-piperidin]-2-one.

[0453] In some embodiments, a compound of formula (I) is selected from the group consisting of:
5-chloro-1'-(2-{[2-(1-methanesulfonylethyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-[(1S)-1-methanesulfonylethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-[(1R)-1-methanesulfonylethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[2-(1-methanesulfonylcyclopropyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-(2-{[2-(1-methanesulfonylcyclopropyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-(difluoromethoxy)-1'-(2-{[2-(1-methanesulfonylcyclopropyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5,7-dichloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
7-chloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-7-carbonitrile;
5-chloro-1'-[(2S)-1-(4-methanesulfonylphenoxy)propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[(2S)-2-(4-methanesulfonylphenoxy)propyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[(2S)-1-(4-methanesulfonylphenoxy)propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[(2S)-2-(4-methanesulfonylphenoxy)propyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[1-(3-methanesulfonylpropyl)-1H-indazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[1-(oxetan-3-yl)-1H-indazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[1-(propan-2-yl)-1H-indazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-(4-{[(cis)-3-hydroxycyclobutyl]sulfonyl}phenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1-(2-hydroxyethyl)-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-(4-methanesulfonylphenoxy)ethyl]-1-[(cis)-3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1-(2-methoxyethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-(4-methanesulfonylphenoxy)ethyl]-1-(2-methoxyethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-chloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1-(oxetan-3-yl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[4-(3-methanesulfonylpropanesulfonyl)phenoxy]ethyl}-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-bromo-1-(2-hydroxyethyl)-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-(4-methanesulfonylphenoxy)ethyl]-1-(2-methoxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1-[2-(4-methanesulfonylphenoxy)ethyl]-1',2'-dihydrospiro[azepane-4,3'-indol]-2'-one;
5-chloro-1'-{2-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[1-(4-methanesulfonylphenoxy)propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1-methyl-1'-{2-[(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1-methyl-1'-{2-[(2-methyl-1-oxo-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1-methyl-1'-{2-[4-(1-methyl-1H-pyrazol-4-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(2-{1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,3-dihydro-1λ⁶-benzothiophene-1,1-dione;
1-methyl-1'-{2-[(1-methyl-2-oxo-2,3-dihydro-1H-indol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1-methyl-1'-[2-(quinoxalin-6-yloxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1-methyl-1'-{2-[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[(1-acetyl-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1-methyl-1'-{2-[4-(2-oxopyrrolidin-1-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-chloro-1'-{2-[4-(1-methanesulfonylethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{4-[(1S)-1-methanesulfonylethyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{4-[(1R)-1-methanesulfonylethyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[4-(3-methanesulfonylpropanesulfonyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-(3,5-difluoro-4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[4-(cyclopropanesulfonyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-(4-difluoromethanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzamide;
4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzamide;
5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)pyridine-2-carboxamide;
5-chloro-1'-[2-(2-fluoro-4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-methylbenzamide;
5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-methanesulfonylbenzonitrile;
5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N,N-dimethylpyridine-2-carboxamide;
4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-methylbenzamide;
5-chloro-1'-{2-[(1-methanesulfonyl-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(2-methanesulfonyl-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[(2-methanesulfonyl-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy]ethyl}-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

1'-{2-[(1-acetyl-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[(2-acetyl-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[(2-acetyl-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy]ethyl}-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[(1-acetyl-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-methyl-1,2,3,4-tetrahydroquinoline-1-carboxamide;
5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-methyl-2,3-dihydro-1H-isoindole-2-carboxamide;
5-chloro-1'-[2-(quinoxalin-6-yloxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-(3-fluoro-4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(6-methanesulfonylpyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(1-methyl-2-oxo-2,3-dihydro-1H-indol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-(4-methanesulfonylphenoxy)ethyl]-5-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-(4-methanesulfonylphenoxy)ethyl]-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(1-methyl-1H-indazol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[(1-methyl-1H-indazol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-(4-methanesulfonylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-bromo-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-``one;
1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

1'-[2-(3-fluoro-4-methanesulfonylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
N-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-N-methylmethanesulfonamide;
N-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-N-methylmethanesulfonamide;
1'-[2-(4-{[dimethyl(oxo)-λ⁶-sulfanylidene]amino}phenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[(8-methyl-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[(8-methyl-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{2-[(8-acetyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[(8-acetyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
2-oxo-1'-{2-[(1,3,3-trimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{2-[3,5-difluoro-4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-({1-[(cis)-3-hydroxycyclobutyl]-1H-indazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({1-[(trans)-3-hydroxycyclobutyl]-1H-indazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-(1H-indazol-5-yloxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(1-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-chloro-1'-[2-(3,5-difluoro-4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-(3,5-difluoro-4-methanesulfonylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
methyl 1-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzenesulfonyl]cyclopropane-1-carboxylate;
5-chloro-1'-(2-{4-[(3-methyloxetan-3-yl)sulfonyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-(2-{4-[(3-methyloxetan-3-yl)sulfonyl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[(2-methanesulfonyl-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
2-oxo-1'-(2-{[2-oxo-1-(propan-2-yl)-1,2,3,4-tetrahydroquinolin-6-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-(2-{[2-oxo-1-(propan-2-yl)-1,2,3,4-tetrahydroquinolin-6-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
N-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-N-(2-hydroxyethyl)methanesulfonamide;
5-chloro-1'-(2-{[1-(oxetan-3-yl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[3-(difluoromethyl)-4-methanesulfonylphenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{2-[4-(1-methanesulfonylcyclopropyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[4-(1-methanesulfonylcyclopropyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-1-methyl-3,4-dihydro-1H-2λ^6,1-benzothiazine-2,2-dione;

1'-{2-[(1-methyl-2,2-dioxo-3,4-dihydro-1H-2λ⁶,1-benzothiazin-6-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-(2-{[1-(2,2-difluoroethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-(2-{[1-(2,2-difluoroethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[4-methanesulfonyl-3-(trifluoromethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[4-methanesulfonyl-3-(trifluoromethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-(4-methanesulfonyl-3-methylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-(4-methanesulfonyl-3-methylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-(4-difluoro-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-(4-difluoromethanesulfonylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-({2-oxo-1-[(cis)-3-hydroxycyclobutyl]-1,2,3,4-tetrahydroquinolin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
(S)-5-chloro-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
(R)-5-chloro-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
2-oxo-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;

(S)-2-oxo-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
(R)-2-oxo-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
(S)-5-chloro-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
(R)-5-chloro-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
2-oxo-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
(S)-2-oxo-1'-(2-((3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-8-yl)oxy)ethyl)spiro[indoline-3,4'-piperidine]-5-carbonitrile;
(R)-2-oxo-1'-(2-((3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-8-yl)oxy)ethyl)spiro[indoline-3,4'-piperidine]-5-carbonitrile;
N-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,6-difluorophenyl]-N-methylmethanesulfonamide;
N-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,6-difluorophenyl]-N-methylmethanesulfonamide;
5-chloro-1'-[2-(4-methanesulfonyl-3,5-dimethylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-(4-methanesulfonyl-3,5-dimethylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{2-[4-(1-methanesulfonylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;

(S)-1'-{2-[4-(1-methanesulfonylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile ;
(R)-1'-{2-[4-(1-methanesulfonylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[3,5-difluoro-4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[3,5-difluoro-4-(1-methanesulfonylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
(S)-1'-{2-[3,5-difluoro-4-(1-methanesulfonylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
(R)-1'-{2-[3,5-difluoro-4-(1-methanesulfonylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{2-[(6-methanesulfonyl-5-methylpyridin-3-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[3,5-difluoro-4-(1-methanesulfonylethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
(S)-5-chloro-1'-{2-[3,5-difluoro-4-(1-methanesulfonylethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
(R)-5-chloro-1'-{2-[3,5-difluoro-4-(1-methanesulfonylethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
2-oxo-1'-(2-{[2-oxo-1-(propan-2-yl)-2,3-dihydro-1H-indol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-(2-{[2-oxo-1-(propan-2-yl)-2,3-dihydro-1H-indol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(2-methyl-1-oxo-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{4-[methyl(methylimino)oxo-λ^6-sulfanyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
(S)-5-chloro-1'-(2-{4-[methyl(methylimino)oxo-λ^6-sulfanyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

(R)-5-chloro-1'-(2-{4-[methyl(methylimino)oxo-λ⁶-sulfanyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-(2-{4-[methyl(methylimino)oxo-λ⁶-sulfanyl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
(S)-1'-(2-{4-[methyl(methylimino)oxo-λ⁶-sulfanyl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
(R)-1'-(2-{4-[methyl(methylimino)oxo-λ⁶-sulfanyl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-methyl-3,4-dihydro-2H-1λ⁶,2-benzothiazine-1,1-dione;
1'-{2-[(2-methyl-1,1-dioxo-3,4-dihydro-2H-1λ⁶,2-benzothiazin-6-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-(3-chloro-4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-(3-chloro-4-methanesulfonylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{2-[4-(1-cyano-1-methylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-({6-[(3-methyloxetan-3-yl)sulfonyl]pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1-(2-hydroxyethyl)-1'-{2-[4-methanesulfonyl-3-(trifluoromethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1-(2-hydroxyethyl)-1'-{2-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(6-methanesulfonyl-5-methylpyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[1-(2-hydroxyethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[3-(difluoromethoxy)-4-methanesulfonylphenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

1'-{2-[3-(difluoromethoxy)-4-methanesulfonylphenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[4-(3-methanesulfonyloxetan-3-yl)-3-(trifluoromethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[4-(3-methanesulfonyloxetan-3-yl)-3-(trifluoromethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-3,4-dihydro-2H-1λ^6,2-benzothiazine-1,1-dione;
1'-{2-[(1,1-dioxo-3,4-dihydro-2H-1λ^6,2-benzothiazin-6-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{2-[(7-fluoro-1-methyl-2-oxo-2,3-dihydro-1H-indol-5-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
2-oxo-1'-{2-[(1-oxo-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[(1-oxo-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-[(3-methyloxetan-3-yl)oxy]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-({2-[(3-methyloxetan-3-yl)oxy]pyrimidin-5-yl}oxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-(2-{4-[3-(ethanesulfonyl)oxetan-3-yl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
2-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-1λ^6-thiolane-1,1-dione;
(S)-2-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-1λ^6-thiolane-1,1-dione;
(R)-2-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-1λ^6-thiolane-1,1-dione;
1'-{2-[4-(1,1-dioxo-1λ^6-thiolan-2-yl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;

5-chloro-1'-(2-{3-oxo-3H-spiro[2-benzofuran-1,3'-oxetan]-5-yloxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[4-(1-methanesulfonylcyclobutyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[4-(1-methanesulfonylcyclobutyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-(4-{6-methanesulfonyl-2-oxaspiro[3.3]heptan-6-yl}phenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-(4-{6-methanesulfonyl-2-oxaspiro[3.3]heptan-6-yl}phenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{2-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-2-oxo-1-(2,2,2-trifluoroethyl)-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-1-(2,2,2-trifluoroethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
N-(4-{2-[5-chloro-1-(2-hydroxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl]ethoxy}-2-(trifluoromethyl)phenyl)methanesulfonamide;
1'-{2-[4-(4-methanesulfonyloxan-4-yl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[4-(4-methanesulfonyloxan-4-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[3,5-difluoro-4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-({7-oxo-8-[(cis)-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-(2-{[6-(2-methanesulfonylpropan-2-yl)pyridin-3-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-(2-{[8-(2-hydroxyethyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
N-{2-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzenesulfonyl]ethyl}-N-methylacetamide;

1'-{2-[(2-acetyl-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy]ethyl}-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,3-dihydro-1λ⁶-benzothiophene-1,1-dione;
5-chloro-1'-{2-[3-(difluoromethyl)-4-methanesulfonylphenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[4-(2-hydroxyethanesulfonyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
chloro-1'-[(2S)-1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
chloro-1'-[(2R)-1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
(S)-1'-{1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
(R)-1'-{1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[1-(4-methanesulfonylphenoxy)propan-2-yl]-1-[3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[(2S)-1-(4-methanesulfonylphenoxy)propan-2-yl]-1-[(cis)-3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[(2S)-1-(4-methanesulfonylphenoxy)propan-2-yl]-1-[(trans)-3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[(2R)-1-(4-methanesulfonylphenoxy)propan-2-yl]-1-[(cis)-3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one ;

5-chloro-1'-[(2R)-1-(4-methanesulfonylphenoxy)propan-2-yl]-1-[(trans)-3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[(2S)-1-[3-(difluoromethyl)-4-methanesulfonylphenoxy]propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[(2S)-1-[(1-methyl-1H-indazol-5-yl)oxy]propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[(2S)-1-[3-(difluoromethyl)-4-methanesulfonylphenoxy]propan-2-yl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-[(2S)-1-(3,5-difluoro-4-methanesulfonylphenoxy)propan-2-yl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
N-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]methanesulfonamide;
5-chloro-1'-[2-(4-{[(trans)-3-hydroxycyclobutyl]sulfonyl}phenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[3-(1,2-dihydroxyethyl)-4-methanesulfonylphenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[3-(1,2-difluoroethyl)-4-methanesulfonylphenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{3-[(1S)-1,2-difluoroethyl]-4-methanesulfonylphenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{3-[(1R)-1,2-difluoroethyl]-4-methanesulfonylphenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[3-(1,2-difluoroethyl)-4-methanesulfonylphenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-(2-{3-[(1S)-1,2-difluoroethyl]-4-methanesulfonylphenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-(2-{3-[(1R)-1,2-difluoroethyl]-4-methanesulfonylphenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[4-methanesulfonyl-3-(oxetan-3-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-chloro-1'-[2-({2-oxo-1-[(trans)-3-hydroxycyclobutyl]-1,2,3,4-tetrahydroquinolin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-(4-{[1-(hydroxymethyl)cyclopropyl]sulfonyl}phenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzenesulfonyl]-N-methylcyclopropane-1-carboxamide;
1-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzenesulfonyl]-N,N-dimethylcyclopropane-1-carboxamide;
1'-[2-(4-{[1-(azetidine-1-carbonyl)cyclopropyl]sulfonyl}phenoxy)ethyl]-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluoro-N-methylbenzamide;
4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluoro-N,N-dimethylbenzamide;
5-chloro-1'-{2-[3-fluoro-4-(morpholine-4-carbonyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
4-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzoyl]-1λ^6-thiomorpholine-1,1-dione;
5-chloro-1'-{2-[3-fluoro-4-(3-methanesulfonylazetidine-1-carbonyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[4-(azetidine-1-carbonyl)-3-fluorophenoxy]ethyl}-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[3-fluoro-4-(3-hydroxyazetidine-1-carbonyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[4-(3-aminoazetidine-1-carbonyl)-3-fluorophenoxy]ethyl}-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
N-{1-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzoyl]azetidin-3-yl}methanesulfonamide;
4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzamide;

6-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzoyl]-2λ⁶-thia-6-azaspiro[3.3]heptane-2,2-dione;
4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-(1,1-dioxo-1λ⁶-thian-4-yl)-2-fluorobenzamide;
4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-(1,1-dioxo-1λ⁶-thiolan-3-yl)-2-fluorobenzamide;
4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-[(3S)-1,1-dioxo-1λ⁶-thiolan-3-yl]-2-fluorobenzamide;
4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-[(3R)-1,1-dioxo-1λ⁶-thiolan-3-yl]-2-fluorobenzamide;
5-chloro-1'-{2-[4-(3-methyl-1H-pyrazol-4-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-methyl-1,2,3,4-tetrahydroisoquinoline-2-carboxamide;
6-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-methyl-1,2,3,4-tetrahydroisoquinoline-2-carboxamide;
5-chloro-1'-[2-({3-methyl-2-oxo-1H,2H,3H-imidazo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(6-{[1-(hydroxymethyl)cyclopropyl]sulfonyl}pyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(difluoromethyl)benzamide;
4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(difluoromethyl)benzamide;
1'-{2-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-(2-{4-[3-(3-fluoroazetidine-1-carbonyl)oxetan-3-yl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-(2-{4-[3-(azetidine-1-carbonyl)oxetan-3-yl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;

3-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-N,N-dimethyloxetane-3-carboxamide;
3-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-N-methyloxetane-3-carboxamide;
5-chloro-1'-{2-[(7-fluoro-2-oxo-2,3-dihydro-1H-indol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
2-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-2-methylpropanamide;
5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)pyrimidine-2-carboxamide;
4-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,6-difluorobenzoyl]-1λ⁶-thiomorpholine-1,1-dione;
1'-{2-[4-(1,1-dioxo-1λ⁶-thiomorpholine-4-carbonyl)-3,5-difluorophenoxy]ethyl}-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{2-[4-(1,1-dioxo-1λ⁶-thiomorpholine-4-carbonyl)-3-(trifluoromethyl)phenoxy]ethyl}-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-{1-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
(S)-1'-{1-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
(R)-1'-{1-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[3-(difluoromethyl)-4-methanesulfonylphenoxy]ethyl}-1-(2-hydroxyethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-{2-[3-(difluoromethyl)-4-methanesulfonylphenoxy]ethyl}-1-(2-hydroxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-({7-oxo-8-[(trans)-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-chloro-1'-(2-{4-[(cis)-3-hydroxy-1-methanesulfonylcyclobutyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{4-[(trans)-3-hydroxy-1-methanesulfonylcyclobutyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
4-(4-{2-[5-chloro-1-(2-hydroxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl]ethoxy}-2-(trifluoromethyl)benzoyl)-1λ⁶-thiomorpholine-1,1-dione;
4-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(trifluoromethyl)benzoyl]-1λ⁶-thiomorpholine-1,1-dione;
5-chloro-1'-[2-(3-fluoro-4-{6-methanesulfonyl-2,6-diazaspiro[3.3]heptane-2-carbonyl}phenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-[2-({7-oxo-8-[(cis)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({7-oxo-8-[(cis)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-oxo-1-[(cis)-3-hydroxy-3-methylcyclobutyl]-1H,2H,4H-pyrido[2,3-d][1,3]oxazin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({7-oxo-8-[(trans)-3-ethyl-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({7-oxo-8-[(trans)-3-cyclopropyl-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[8-(3-cyclopropyl-3-hydroxycyclobutyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[8-(3-hydroxy-3-methylazetidin-1-yl)-1,7-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({7-oxo-8-[(trans)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-[2-({7-oxo-8-[(cis)-3-(hydroxymethyl)cyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-(difluoromethyl)-1'-[2-({7-oxo-8-[(trans)-3-(hydroxymethyl)cyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-{2-[(7-oxo-8-{[(cis)-3-hydroxy-3-methylcyclobutyl]methyl}-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-{2-[(7-oxo-8-{[(trans)-3-hydroxy-3-methylcyclobutyl]methyl}-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(7-oxo-8-{[(cis)-3-hydroxy-3-methylcyclobutyl]methyl}-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[8-(3-hydroxyazetidin-1-yl)-1,7-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[8-(3-hydroxy-3-methylcyclobutyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-[2-({8-[3-(hydroxymethyl)cyclobutyl]-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one ;
5-chloro-1'-[2-({7-oxo-8-[(cis)-3-hydroxy-3-(propan-2-yl)cyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[8-(3-ethyl-3-hydroxycyclobutyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({7-oxo-8-[(cis)-3-(hydroxymethyl)cyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one ;
5-(difluoromethyl)-1'-[2-({8-[(3-hydroxy-3-methylcyclobutyl)methyl]-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({7-oxo-8-[(cis)-3-ethyl-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(7-oxo-8-{[(trans)-3-hydroxy-3-methylcyclobutyl]methyl}-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({7-oxo-8-[(cis)-3-hydroxy-3-methylcyclobutyl]-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-[2-({7-oxo-8-[(cis)-3-hydroxy-3-methylcyclobutyl]-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-(difluoromethoxy)-1'-[2-({7-oxo-8-[(cis)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({8-[3-(hydroxymethyl)cyclobutyl]-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({8-[(3-hydroxy-3-methylcyclobutyl)methyl]-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethoxy)-1'-[2-({7-oxo-8-[(cis)-3-hydroxy-3-methylcyclobutyl]-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-7-iodo-1'-[2-({7-oxo-8-[(cis)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({7-oxo-8-[(trans)-3-hydroxy-3-(propan-2-yl)cyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({7-oxo-8-[(trans)-3-(hydroxymethyl)cyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-(2-{[6-(1-hydroxyethyl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one ;
1'-(2-{[6-(1-hydroxyethyl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-(2-{[5-(difluoromethyl)-7-oxo-8-[(cis)-3-hydroxy-3-methylcyclobutyl]-7,8-dihydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-(2-{[5-(difluoromethyl)-7-oxo-8-[(cis)-3-hydroxy-3-methylcyclobutyl]-7,8-dihydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({7-oxo-8-[(cis)-3-hydroxy-3-methylcyclobutyl]-5-(trifluoromethyl)-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-[2-({7-oxo-8-[(cis)-3-hydroxy-3-methylcyclobutyl]-5-(trifluoromethyl)-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-oxo-1-[(cis)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-[2-({2-oxo-1-[(cis)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-chloro-1'-[2-({2-oxo-1-[(trans)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-[2-({2-oxo-1-[(trans)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one ;
5-chloro-1'-[2-({1-[(cis)-3-hydroxy-3-methylcyclobutyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-[2-({1-[(cis)-3-hydroxy-3-methylcyclobutyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-oxo-1-[(cis)-3-hydroxy-3-methylcyclobutyl]-1H,2H-pyrido[2,3-d]pyrimidin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-oxo-1-[(cis)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H,4H-pyrido[2,3-d]pyrimidin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({1-[(cis)-3-hydroxy-3-methylcyclobutyl]-1H-pyrazolo[3,4-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({3-oxo-4-[(cis)-3-hydroxy-3-methylcyclobutyl]-3H,4H-pyrido[2,3-b]pyrazin-7-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[4-(3-hydroxy-3-methylcyclobutyl)pyrido[3,2-d]pyrimidin-7-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[8-(3-hydroxy-3-methylcyclobutyl)-1,7-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[8-(3-hydroxy-3-methylazetidin-1-yl)pyrido[2,3-d]pyridazin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[4-(3-hydroxy-3-methylazetidin-1-yl)pyrido[3,2-d]pyrimidin-7-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[8-(3-hydroxyazetidin-1-yl)pyrido[2,3-d]pyridazin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[4-(3-hydroxyazetidin-1-yl)pyrido[3,2-d]pyrimidin-7-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({3-[(cis)-3-hydroxy-3-methylcyclobutyl]-3H-imidazo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one ;

5-chloro-1'-[2-({2-oxo-3-[(cis)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H-imidazo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({8-[3-(hydroxymethyl)azetidin-1-yl]-1,7-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-({6-[(1S)-1-hydroxyethyl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3 ,4'-piperidine]-5-carbonitrile ;
1'-[2-({6-[(1R)-1-hydroxyethyl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-({2-[(1S)-1,2-dihydroxyethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-[(1R)-1,2-dihydroxyethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-[(2S)-1,2-dihydroxypropan-2-yl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-[(2R)-1,2-dihydroxypropan-2-yl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({6-[(1S)-1,2-dihydroxyethyl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({6-[(1R)-1,2-dihydroxyethyl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({6-[(2S)-1,2-dihydroxypropan-2-yl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({6-[(2R)-1,2-dihydroxypropan-2-yl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({8-[(cis)-3-hydroxy-3-methylcyclobutyl]-1,7-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({8-[(trans)-3-hydroxy-3-methylcyclobutyl]-1,7-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({4-[(cis)-3-hydroxy-3-methylcyclobutyl]pyrido[3,2-d]pyrimidin-7-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-chloro-1'-[2-({4-[(trans)-3-hydroxy-3-methylcyclobutyl]pyrido[3,2-d]pyrimidin-7-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({8-[(cis)-3-hydroxy-3-methylcyclobutyl]pyrido[2,3-d]pyridazin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({8-[(trans)-3-hydroxy-3-methylcyclobutyl]pyrido[2,3-d]pyridazin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-[(cis)-3-hydroxy-3-methylcyclobutyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-[(trans)-3-hydroxy-3-methylcyclobutyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-oxo-3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-2H,3H-[1,3]oxazolo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-(2-{[2-(3-hydroxy-3-methylazetidin-1-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(2-{6-hydroxy-2-azaspiro[3.3]heptan-2-yl}pyrimidin-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[2-(3-ethyl-3-hydroxyazetidin-1-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-cyclopropyl-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[6-(1-hydroxyethyl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5,7-dichloro-1'-(2-{[2-(1-methanesulfonylcyclopropyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[2-(1,2-dihydroxyethyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-[1-(hydroxymethyl)cyclopropyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[2-(1-hydroxy-2-methylpropan-2-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-chloro-1'-(2-{[5-(difluoromethyl)-7-oxo-8-[(cis)-3-hydroxy-3-methylcyclobutyl]-7,8-dihydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-(2-{[5-(difluoromethyl)-7-oxo-8-[(cis)-3-hydroxy-3-methylcyclobutyl]-7,8-dihydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({7-oxo-8-[(cis)-3-hydroxy-3-methylcyclobutyl]-5-(trifluoromethyl)-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-[2-({7-oxo-8-[(cis)-3-hydroxy-3-methylcyclobutyl]-5-(trifluoromethyl)-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{4-[1-(dimethylphosphoryl)cyclopropyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-[1-(dimethylphosphoryl)cyclopropyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-oxo-1-[(1r,3s)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-[2-({2-oxo-1-[(cis)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({1-[(cis)-3-hydroxy-3-methylcyclobutyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({1-[(cis)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-oxo-1-[(cis)-3-hydroxy-3-methylcyclobutyl]-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
2-oxo-1'-[2-({2-oxo-1-[(cis)-3-hydroxy-3-methylcyclobutyl]-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-({2-oxo-1-[(1r,3s)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H,4H-pyrido[2,3-d]pyrimidin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({1-[(cis)-3-hydroxy-3-methylcyclobutyl]-1H-pyrazolo[3,4-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({3-oxo-4-[(cis)-3-hydroxy-3-methylcyclobutyl]-3H,4H-pyrido[2,3-b]pyrazin-7-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-chloro-1'-[2-({3-[(cis)-3-hydroxy-3-methylcyclobutyl]-3H-imidazo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[6-(2-hydroxypropan-2-yl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[2-(3-hydroxy-3-methylcyclobutyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-oxo-3-[(cis)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H-imidazo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-[(1R or 1S)-1,2-dihydroxyethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one ;
5-chloro-1'-[2-({2-[(1S or 1R)-1,2-dihydroxyethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-[(cis)-3-hydroxy-3-methylcyclobutyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-[(cis) or (trans)-3-hydroxy-3-methylcyclobutyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[6-(1-hydroxy-2-methanesulfonylpropan-2-yl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({6-[(2S or 2R)-1-hydroxy-2-methanesulfonylpropan-2-yl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({6-[(2R or 2S)-1-hydroxy-2-methanesulfonylpropan-2-yl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
2-oxo-1'-[2-({7-oxo-8-[(cis)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-(2-{[6-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
2-oxo-1'-[2-({7-oxo-8-[(cis)-3-hydroxy-3-methylcyclobutyl]-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-1H-pyrazolo[3,4-b]pyridin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-chloro-1'-[2-({1-[(trans)-3-hydroxy-3-methylcyclobutyl]-1H-pyrazolo[3,4-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5,7-dichloro-1'-[2-({7-oxo-8-[(cis)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
2-oxo-1'-[2-({1-[(cis)-3-hydroxy-3-methylcyclobutyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-(2-{[6-(2-hydroxypropan-2-yl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[4-(1-methanesulfonylpiperidin-4-yl)phenoxy]ethyl}-1-($^{2}H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1-($^{2}H_3$)methyl-1'-(2-{4-[methyl(methylimino)oxo-λ^6-sulfanyl]-3-(trifluoromethyl)phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1-($^{2}H_3$)methyl-1'-(2-{4-[3-(propane-2-sulfonyl)oxetan-3-yl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[4-(1-methanesulfonylcyclobutyl)phenoxy]ethyl}-1-($^{2}H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1-($^{2}H_3$)methyl-1'-{2-[(2-methyl-1-oxo-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[8-(2-hydroxy-2-methylpropyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1-($^{2}H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1-($^{2}H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1-($^{2}H_3$)methyl-1'-[2-({7-oxo-8-[(cis)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-[1-(hydroxymethyl)cyclopropyl]pyrimidin-5-yl}oxy)ethyl]-1-($^{2}H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
6-{2-[5-chloro-1-($^{2}H_3$)methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl]ethoxy}-8-fluoro-3,4-dihydro-2H-1λ^6,2-benzothiazine-1,1-dione;
5-chloro-1'-(2-{[2-(3-methanesulfonyloxetan-3-yl)pyrimidin-5-yl]oxy}ethyl)-1-($^{2}H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-chloro-1-($^{2}H_3$)methyl-1'-[2-({7-oxo-8-[(cis)-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[2-(1-methanesulfonylcyclopropyl)pyrimidin-5-yl]oxy}ethyl)-1-($^{2}H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[2-(1-methanesulfonylethyl)pyrimidin-5-yl]oxy}ethyl)-1-($^{2}H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({7-oxo-8-[(cis)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)(1,1,2,2-$^{2}H_4$)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-[(cis)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2H-indazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
2-oxo-1'-[2-({2-[(cis)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2H-indazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-(2-{[2-(3-hydroxyoxetan-3-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[2-(1-hydroxycyclobutyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-(2-{[6-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-(2-{[2-(1-hydroxy-2-methylpropan-2-yl)pyrimidin-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
2-oxo-1'-[2-({1-[(cis)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-({1-[(cis)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,2,3-benzotriazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
2-oxo-1'-[2-({1-[(cis)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,2,3-benzotriazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-1H-pyrazolo[3,4-b]pyridin-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
2-oxo-1'-[2-({1-[(cis)-3-hydroxy-3-methylcyclobutyl]-1H-pyrazolo[3,4-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;

1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-1H-pyrazolo[3,4-b]pyridin-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-1-[(cis)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazole-7-carbonitrile;
5-chloro-1'-[2-({3-[(cis)-3-hydroxy-3-methylcyclobutyl]-3H-[1,2,3]triazolo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[2-(2,2-dimethyl-1,3-dioxolan-4-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-methyl-1-[(cis)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-({2-methyl-1-[(cis)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-{2-[4-(1-methanesulfonylpiperidin-4-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[7-(difluoromethyl)-1-[(cis)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-(2-{[7-(difluoromethyl)-1-[(cis)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-(2-{[7-(difluoromethoxy)-1-[(cis)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-(2-{[7-(difluoromethoxy)-1-[(cis)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-(2-{[2-(2-hydroxypropan-2-yl)pyrimidin-5-yl]oxy}ethyl)-7-iodo-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-(difluoromethyl)-1'-[2-({1-[(cis)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-methyl-3-[(cis)-3-hydroxy-3-methylcyclobutyl]-3H-imidazo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{[8-(2-hydroxy-2-methylpropyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-chloro-7-iodo-1'-[2-({1-[(cis)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({7-fluoro-1-[(cis)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-[2-({7-fluoro-1-[(cis)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-({2-oxo-1-[(cis)-3-hydroxy-3-methylcyclobutyl]-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinazolin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
2-oxo-1'-[2-({2-oxo-1-[(cis)-3-hydroxy-3-methylcyclobutyl]-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinazolin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-({7,7-dimethyl-5-oxo-5H,7H-furo[3,4-b]pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-{2-[(2-{6-hydroxy-6-methyl-2-azaspiro[3.3]heptan-2-yl}pyrimidin-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{2'-oxo-1'-[(cis)-3-hydroxy-3-methylcyclobutyl]-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-5'-yloxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({7-oxo-8-[(cis)-3-hydroxy-3-($^{2}H_3$)methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({7-oxo-8-[(cis)-3-hydroxy-3-($^{2}H_3$)methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)(1,1,2,2-$^{2}H_4$)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({1-[(cis)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)(1,1,2,2-$^{2}H_4$)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({1-[(cis)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-indazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
2-oxo-1'-[2-({1-[(cis)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-indazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-({2-[(1r,3s)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;

5-chloro-1'-(2-{[3-(hydroxymethyl)-2-oxo-1-[(cis)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2,3-dihydro-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-[2-({2-oxo-1-[(cis)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2,3-dihydro-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
1'-(2-{[3-(hydroxymethyl)-2-oxo-1-[(cis)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2,3-dihydro-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
2-oxo-1'-[2-({2-oxo-1-[(cis)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2,3-dihydro-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile;
5-chloro-1'-[2-({1-[(cis)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-imidazo[4,5-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one;
5-chloro-1'-(2-{3-[(cis)-3-hydroxy-3-methylcyclobutyl]-4-(trifluoromethyl)-3H-1,3,5-triazainden-6-yloxy}ethyl)spiro[indoline-3,4'-piperidin]-2-one,
or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0454] Isotopically labeled forms of any of the foregoing are also embraced, such as deuterated or tritiated forms (wherein at least one hydrogen is replaced by at least one deuterium or tritium) of any of the specific compounds detailed herein. Mixtures of any of the foregoing are also embraced and described. Prodrugs of any of the foregoing are also embraced herein.

[0455] As a non-limiting example, compounds of formula (II), formula (I'), or formula (I), or any embodiment or variation thereof, are provided, wherein any one or more H atoms are replaced with deuterium. For example, compounds of formula (II), formula (I'), or formula (I), or any embodiment or variation thereof, are provided wherein L^1 is $C_{1\text{-}6}$alkylene, wherein one or more H atoms of the $C_{1\text{-}6}$alkylene are replaced with deuterium. For example, compounds of formula (II), formula (I'), or formula (I), or any embodiment or variation thereof, are provided wherein L^1 is $-(CD_2)_{1\text{-}6}-$. In some embodiments of formula (II), formula (I'), or formula (I), or any embodiment or variation thereof, L^1 is $-(CD_2)-(CD_2)-$.

[0456] In some embodiments, compounds of formula (II), formula (I'), or formula (I) contain one or more hydrogen atoms that are replaced with deuterium, wherein deuterium is present in an amount that is greater than its natural abundance. Thus, as used herein, designation of an atom as

deuterium at a position indicates that the abundance of deuterium is significantly greater than the natural abundance of deuterium. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen," the position is understood to have hydrogen at its naturally abundant isotopic composition. Also, unless otherwise stated, when a position is designated specifically as "D" or "deuterium," the position is understood to have deuterium at an abundance that is significantly greater than the natural abundance of deuterium, e.g., at least 3000 times greater than the natural abundance of deuterium, which is about 0.015% (i.e., the term "D" or "deuterium" indicates at least about 45% incorporation of deuterium).

[0457] Compound Names included in Table 1 and in the list in the paragraph above were generated ChemDraw® software version 18.1.0.458, ChemDraw® software version 18.0.0.231, or Collaborative Drug Discovery Inc. (CDD) CDD Vault update #3.

COMPOSITIONS

[0458] Provided herein are pharmaceutical compositions comprising one or more compounds of formula (II), formula (I), formula (I'), or any variation or embodiment thereof, as described elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing. In some embodiments, provided herein is a pharmaceutical composition comprising (i) a compound of formula (II), formula (I), formula (I') or any variation or embodiment thereof, as described elsewhere 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.

[0459] Suitable pharmaceutically acceptable excipients may include, for example, fillers, diluents, sterile aqueous solutions and various organic solvents, permeation enhancers, solubilizers, and adjuvants. Various substances may be embraced by the term excipient, including without limitation any substance used as a binder, disintegrant, coating, compression/encapsulation aid, cream or lotion, lubricant, solutions for parenteral administration, materials for chewable tablets, sweetener or flavoring, suspending/gelling agent, or wet granulation agent. Examples of suitable excipients are well-known to those skilled in the art. Such compositions are prepared in a manner well known in the pharmaceutical art. *See*, *e.g.*, *Remington's Pharmaceutical Sciences*, Academic Press, 23rd ed. (2020), which is incorporated herein by reference.

[0460] The pharmaceutical compositions may be administered in either single or multiple doses. The pharmaceutical composition may be administered by various methods including, for example, oral, rectal, buccal, intranasal, and transdermal routes. In certain embodiments, the pharmaceutical composition may be administered by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, or as an inhalant.

[0461] Compounds as described herein may be administered to individuals in a form of generally accepted oral compositions, such as tablets, coated tablets, gel capsules in a hard or in soft shell, emulsions or suspensions. Examples of carriers, which may be used for the preparation of such compositions, are lactose, corn starch or its derivatives, talc, stearate or its salts, etc. Acceptable carriers for gel capsules with soft shell are, for instance, plant oils, wax, fats, semisolid and liquid poly-ols, and so on. In addition, pharmaceutical formulations may contain preservatives, solubilizers, stabilizers, re-wetting agents, emulgators, sweeteners, dyes, adjusters, salts for the adjustment of osmotic pressure, buffers, coating agents or antioxidants.

[0462] The specific dose level of a compound as described herein will depend upon a variety of factors such as the age, body weight and sex of the individual as well as the route of administration and other factors. In some embodiments, a dosage is expressed as a number of milligrams of a compound described herein per kilogram of the individual's body weight (mg/kg). Dosages of between about 0.1 mg/kg and 100-150 mg/kg may be appropriate.

[0463] The compound may be administered to an individual in accordance with an effective dosing regimen for a desired period of time or duration, such as at least about one month, at least about 2 months, at least about 3 months, at least about 6 months, or at least about 12 months or longer, which in some variations may be for the duration of the individual's life.

METHODS OF TREATMENT

[0464] Provided herein is a method of modulating APOL1 in a cell, comprising exposing the cell to an effective amount of a compound of formula (I), formula (I'), formula (II), or any variation or embodiment thereof, as described elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing. Also 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 (I), formula (I'), formula (II), or any variation or embodiment

thereof, as described elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients. Isotopically labeled forms of any of the foregoing are also embraced, including, but not limited to, deuterated or tritiated forms (wherein at least one hydrogen is replaced by at least one deuterium, or tritium) of any of the specific compounds detailed herein.

[0465] Provided herein is a method of inhibiting APOL1 in a cell, comprising exposing the cell to an effective amount of a compound of formula (I), formula (I'), formula (II), or any variation or embodiment thereof, as described elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing. Also provided herein is a method of inhibiting APOL1 in a cell, comprising exposing the cell to a pharmaceutical composition comprising an effective amount of a compound of formula (I), formula (I'), formula (II), or any variation or embodiment thereof, as described elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients.

[0466] Provided herein is a method of inhibiting APOL1 in an individual, comprising administering to the individual an effective amount of a compound of formula (I), formula (I'), or any variation or embodiment thereof, as described elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing. Also provided herein is a method of inhibiting APOL1 in an individual, comprising administering to the individual a pharmaceutical composition comprising an effective amount of a compound of formula (I), formula (I'), formula (II), or any variation or embodiment thereof, as described elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients.

[0467] In some embodiments, the compounds provided herein inhibit APOL1 at a concentration of less than 10 μM, less than 1 μM, less than 0.5 μM, or less than 0.1 μM. In some embodiments, the compounds provided herein inhibit APOL1 at a concentration of 1 to 10 μM, 0.01 to 1 μM, or 0.01 to 10 μM.

[0468] In some embodiments, the compounds provided herein reduce cell death caused by overexpression of APOL1. In some embodiments, the compounds provided herein reduce cell death caused by overexpression APOL1 at a concentration of less than 10 μM, less than 1 μM, less than

0.5 μM, or less than 0.1 μM. In some embodiments, the compounds provided herein reduce cell death caused by APOL1 overexpression at a concentration of 1 to 10 μM, 0.01 to 1 μM, or 0.01 to 10 μM.

[0469] In some embodiments, compounds provided herein have an EC_{50} of less than 1 μM, less than 0.5 μM, or less than 0.1 μM. In some embodiments, the compounds provided herein have an EC_{50} of 1 to 10 μM, 0.01 to 1 μM, or 0.01 to 10 μM.

[0470] In some embodiments, compounds provided herein have an AC_{50} of less than 1 μM, less than 0.5 μM, or less than 0.1 μM. In some embodiments, the compounds provided herein have an AC_{50} of 1 to 10 μM, 0.01 to 1 μM, or 0.01 to 10 μM. In some embodiments, the AC_{50} value reflects the compound's ability to prevent calcium influx by inhibiting APOL1.

[0471] In some embodiments, the compounds provided herein inhibit a cation channel. In some embodiments, the compounds of the present disclosure inhibit a calcium channel. In some embodiments, the compounds of the present disclosure reduce calcium transport.

[0472] 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 a therapeutically effective amount of a compound of formula (I), formula (I'), formula (II), or any variation or embodiment thereof, as described elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing. Also 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 a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I), formula (I'), formula (II), or any variation or embodiment thereof, as described elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients.

[0473] Provided herein is a method of treating a kidney disease, disorder, or condition in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of formula (I), formula (I'), formula (II), or any variation or embodiment thereof, as described elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing. Also provided herein is a method of treating a kidney disease, disorder, or condition in an individual in need thereof, comprising administering to the

individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I), formula (I'), formula (II), or any variation or embodiment thereof, as described elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients.

[0474] In some embodiments, the individual has a chronic kidney disease. In some embodiments, the individual has hypertension-attributed kidney disease. In some embodiments, the kidney disease, disorder, or condition is an APOL1-mediated kidney disease, disorder, or condition. In some embodiments, the kidney disease, disorder, or condition is selected from the group consisting of focal segmental glomerulosclerosis (FSGS), hypertension-attributed kidney disease, viral nephropathy, COVID-19 associated nephropathy, human immunodeficiency virus-associated nephropathy (HIVAN), sickle-cell nephropathy, lupus nephritis, and diabetic kidney disease.

[0475] Also provided herein is a method of treating an APOL1-mediated disorder, such as preeclampsia and sepsis, comprising administering to an individual in need thereof a therapeutically effective amount of a compound of formula (I), formula (I'), formula (II), or any variation or embodiment thereof, as described elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing. In some embodiments, the individual is genetically predisposed to developing the APOL1-mediated disorder.

[0476] Also provided herein is a method of delaying development of progressive renal allograft loss in a kidney transplant recipient comprising administering to the kidney transplant recipient a therapeutically effective amount of a compound of formula (I), formula (I'), or any variation or embodiment thereof, as described elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing. In some embodiments, the kidney transplant recipient receives a kidney from a high-risk APOL1 genotype donor. In some embodiments, the kidney transplant recipient is administered a therapeutically effective amount of the compound for a period of time before receiving the kidney transplant. In some embodiments, the kidney transplant recipient is administered a therapeutically effective amount of the compound subsequent to receiving the kidney transplant.

[0477] Provided herein is a method of treating a kidney disease, disorder, or condition in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of formula (I), formula (I'), formula (II), or any variation or embodiment

thereof, as described elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the individual has an APOL1 mutation. Also provided herein is a method of treating a kidney disease, disorder, or condition in an individual in need thereof, comprising administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I), formula (I'), formula (II), or any variation or embodiment thereof, as described elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients, wherein the individual has an APOL1 mutation.

[0478] The compounds provided herein may also be used in a method of delaying the development of an APOL1-mediated disease, disorder, or condition, comprising administering a compound of formula (I), formula (I'), formula (II), or any variation or embodiment thereof, as described elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, to an individual who is at risk of developing an APOL1-mediated disease, disorder, or condition. In some embodiments, the APOL1-mediated disease, disorder, or condition is preeclampsia or sepsis and the individual has two APOL1 risk alleles. In some embodiments, the APOL1-mediated disease, disorder, or condition is a chronic kidney disease and the individual has any binary combination of G1 and G2 APOL1 risk alleles. In some embodiments, the chronic kidney disease is focal segmental glomerulosclerosis (FSGS), hypertension-attributed kidney disease, human immunodeficiency virus-associated nephropathy (HIVAN), hypertension-attributed kidney disease, sickle cell nephropathy, viral nephropathy, COVID-19 associated nephropathy, lupus nephritis, diabetic kidney disease, or APOL1-associated nephropathy. The compounds as provided herein may also be used in a method of delaying the development of progressive renal allograft loss in an individual who has received a kidney transplantation from a high-risk APOL1 genotype donor.

[0479] In some embodiments, the individual has a gain-of-function mutation in APOL1. In some embodiments, the individual has an APOL1 risk allele. In some embodiments, the APOL1 risk allele is a missense variant. In some embodiments, the APOL1 risk allele is a G1 variant. In some embodiments, the G1 variant is $G1^{G}$ (p.S342 G) or $G1^{M}$ (p.I384 M). In some embodiments, the APOL1 risk allele is the G2 variant. In some embodiments, the G2 variant is NYK388–389K. In some embodiments, the APOL1 risk variant is a mutation in the serum resistance-associated

(SRA) binding domain of the APOL1 protein. In some embodiments, the individual has two APOL1 risk alleles.

[0480] Also provided herein is a method of inhibiting APOL1 in an individual comprising administering to the individual a therapeutically effective amount of a compound of formula (I), formula (I'), formula (II), or any variation or embodiment thereof, as described elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0481] Also provided herein is method of preventing kidney failure in an individual comprising administering a therapeutically effective amount of a compound of formula (I), formula (I'), formula (II), or any variation or embodiment thereof, as described elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing to the individual. In some embodiments, the compound prevents tissue necrosis. In some embodiments, the compound prevents apoptosis. In some embodiments, the compound reduces inflammation.

[0482] In some embodiments, the compounds provided herein reduce or eliminate one or more symptoms of a kidney disease. In some embodiments, the compounds reduce nausea, vomiting, loss of appetite, fatigue and weakness, sleep problems, urinary frequency issues, muscle twinges and cramps, swelling, itching, chest pain, shortness of breath, and/or high blood pressure.

[0483] In some embodiments, the compounds provided herein reduce the rate of kidney damage and/or progression of kidney damage. In some embodiments, the compounds provided herein reduce the rate of kidney failure. In some embodiments, the compounds provided herein reverse kidney damage. In some embodiments, the compounds reduce the need for dialysis. In some embodiments, the compounds provided herein delay the need for dialysis at least one month, at least two months, at least three months, or at least one year.

[0484] In some embodiments, the compounds reduce the rate of or delay the need for a kidney transplant. For example, in some embodiments, the compounds provided herein delay the need for a kidney transplant at least one month, at least two months, at least three months, at least six months, or at least one year. In some embodiments, the compounds provided herein eliminate the need for a kidney transplant.

[0485] In some embodiments, the individual has stage 1, stage 2, stage 3A, stage 3B, stage 4, or stage 5 chronic kidney disease. In some embodiments, kidney function is evaluated using an estimated glomerular filtration rate (eGFR) kidney function test.

[0486] The compounds and compositions comprising the compounds provided herein may also be used in a method of delaying or preventing proteinuria, the method comprising administering the compound, or any variation or embodiment thereof, as described elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, to an individual. In one aspect, the methods herein comprise preventing or reducing protein in the urine, e.g., proteinuria. In some embodiments, the methods provided herein prevent proteinuria. In some embodiments, the methods reduce proteinuria. In some embodiments, the methods provided herein prevent albuminuria. In some embodiments, the methods reduce albuminuria. In some embodiments, the methods reduce urine albumin. In some embodiments, urine albumin is reduced by at least about 50%, about 60%, about 70%, about 80%, or about 90%, or greater. In some embodiments, urine albumin is reduced by at least about 50%. In some embodiments, urine albumin is reduced by at least about 60%. In some embodiments, urine albumin is reduced by at least about 70%. In some embodiments, urine albumin is reduced by at least about 80%. In some embodiments, urine albumin is reduced by at least about 90%. In some embodiments, reduction of urine albumin is dose-dependent. In some embodiments, the methods provided herein reduce urine albumin/creatine ratio. In some embodiments, urine albumin/creatine ratio is reduced by at least about 50%, about 60%, about 70%, about 80%, or about 90%, or greater. In some embodiments, urine albumin/creatine ratio is reduced by at least about 50%. In some embodiments, urine albumin/creatine ratio is reduced by at least about 60%. In some embodiments, urine albumin/creatine ratio is reduced by at least about 70%. In some embodiments, urine albumin/creatine ratio is reduced by at least about 80%. In some embodiments, urine albumin/creatine ratio is reduced by at least about 90%. In some embodiments, reduction of urine albumin/creatine ratio is dose-dependent. In some embodiments, the reduction and/or ratios are measured according to assays detailed herein. In any of the aforementioned methods, the individual is an individual in need thereof, such as an individual having an APOL1-mediated disease, disorder, or condition. In some embodiments, the APOL1-mediated disease, disorder, or condition is a kidney disease. In some embodiments, the APOL1-mediated disease, disorder, or condition is a chronic kidney disease. In some embodiments, the individual has hypertension-attributed kidney disease. In some embodiments, the kidney disease, disorder, or condition is selected from the group consisting of focal segmental glomerulosclerosis (FSGS), hypertension-attributed kidney disease,

viral nephropathy, COVID-19 associated nephropathy, human immunodeficiency virus-associated nephropathy (HIVAN), sickle-cell nephropathy, lupus nephritis, and diabetic kidney disease.

[0487] In some embodiments, the administration is oral administration.

KITS

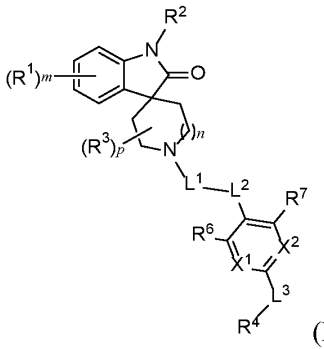
[0488] The present disclosure further provides kits for carrying out the methods of the invention. The kits may comprise a compound or pharmaceutically acceptable salt thereof as described herein and suitable packaging. The kits may comprise one or more containers comprising any compound described herein. In one aspect, a kit includes a compound of the disclosure or a pharmaceutically acceptable salt thereof, and a label and/or instructions for use of the compound in the treatment of a disease or disorder described herein. The kits may comprise a unit dosage form of the compound.

[0489] Provided herein are kits, comprising (i) a compound of formula (I), formula (I'), formula (II), or any variation or embodiment thereof, as described elsewhere herein, 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. Also provided herein are kits, comprising (i) a pharmaceutical composition comprising a compound of formula (I), or any variation or embodiment thereof, as described elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients; and (ii) instructions for use in treating an APOL1-mediated disease, disorder, or condition in an individual in need thereof.

[0490] Articles of manufacture are also provided, wherein the article of manufacture comprises a compound of formula (I), formula (I'), formula (II), or any variation or embodiment thereof, as described elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, in a suitable container. Also provided herein are articles of manufacture, comprising a pharmaceutical composition comprising a compound of formula (I), formula (I'), formula (II), or any variation or embodiment thereof, as described elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, in a suitable container. The container may be a vial, jar, ampoule, preloaded syringe, or intravenous bag.

ENUMERATED EMBODIMENTS

[0491] Embodiment 1A. A compound of formula (I):



(I),

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

m is an integer from 0 to 4;

n is an integer from 0 to 2;

p is an integer from 0 to 10;

R^1, if present is, independently at each occurrence selected from the group consisting of halo, -CN, C_{1-6}alkoxy, or -C_{1-6}alkyl, wherein

the C_{1-6}alkoxy of R^1 is optionally substituted with one or more halo, and

the C_{1-6}alkyl of R^1 is optionally substituted with one or more halo;

R^2 is H, C_{1-6}alkyl, C_{3-10}cycloalkyl, or 3-15 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^2 is optionally substituted with one or more halo, -OH, -NH_2, or C_{1-6}alkoxy, and

the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more -OH;

R^3, if present, is C_{1-6}alkyl;

L^1 is C_{1-6}alkylene, wherein the C_{1-6}alkylene of L^1 is optionally substituted with one or more C_{1-6}alkyl, and wherein the C_{1-6}alkyl is further optionally substituted with one or more -OH or C_{1-6}alkoxy;

L^2 is O or N(R^x), wherein R^x is H or C_{1-6}alkyl; and

either

(1) L^3 is absent or is O, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or C_{1-6}alkylene, wherein

the C_{1-6}alkylene of L^3 is optionally substituted with one or more C_{1-6}alkyl, and

the 3-10 membered heterocyclyl is optionally substituted with one or more –OH;

X^1 and X^2 are each independently N or $C(R^5)$; and

R^4 is:

(i) $-S(O)_2-R^a$;

(ii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^4 is optionally substituted with one or more C_{1-6}alkyl;

(iii) $-N(R^d)_2$, wherein R^d is independently at each occurrence H, C_{1-6} alkyl, or $-S(O)_2-R^a$, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more –OH,

(iv) $-NS(O)-(C_{1-6}alkyl)_2$, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more –OH,

(v) $-C(O)-N(R^e)_2$ wherein R^e is independently at each occurrence H, C_{1-6} alkyl, or 3-10 membered heterocycle, wherein the 3-10 membered heterocycle is optionally substituted with one or more oxo, or both R^e together with the N to which they are attached are taken together to form a 3-10 membered heterocyclyl, wherein the 3-10 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, $NH-S(O)_2-R^a$, or $-S(O)_2-R^a$,

(vi) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl or oxo,

(vii) $-S(O)-N(C_{1-6}alkyl)-(C_{1-6}alkyl)$,

(viii) –CN;

or

(2) L^3 is absent; and

one of X^1 and X^2 is N or $C(R^5)$; and

the other of X^1 and X^2 is N or C that is taken together with R^4, and the atoms to which they are attached, to form a 5-10 membered heterocyclyl or a 5-20 membered heteroaryl, wherein

the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is, independently at each occurrence, selected from the group consisting of halo, oxo, C_{1-6}alkyl, $-C(O)-C_{1-6}$alkyl, $-C(O)-NH_2$, $-C(O)-NH(C_{1-6}alkyl)$, $-C(O)-N(C_{1-6}alkyl)_2$, $-S(O)_2-R^a$, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, OH, or -$S(O)_2$-C_{1-6}alkyl, and

the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more -OH, and

the 5-20 membered heteroaryl is optionally substituted with one or more R^c, wherein

R^c is, independently at each occurrence, selected from the group consisting of halo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -$S(O)_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more -$S(O)_2$-C_{1-6}alkyl, and

the C_{3-10}cycloalkyl of R^c is optionally substituted with one or more -OH;

R^a is, independently at each occurrence:

(i) C_{1-6}alkyl optionally substituted with one or more halo, -OH, -$S(O)_2$-C_{1-6}alkyl, or -N(C_{1-6}alkyl)-C(O)-C_{1-6}alkyl, or

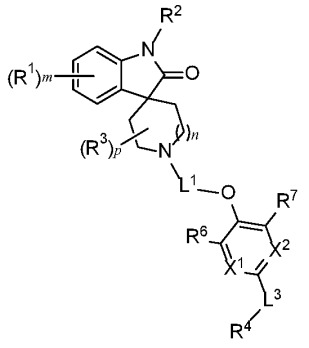
(ii) C_{3-10}cycloalkyl optionally substituted with one or more -OH, -$C(O)_2$-C_{1-6}alkyl, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, or –C(O)-C_{3-10}heterocyclyl, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more -OH, or

(iii) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl;

R^5 is, independently at each occurrence, H, halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH and wherein the C_{1-6}alkoxy is optionally substituted with one or more halo; and

R^6 and R^7 are each independently H or halo.

[0492] Embodiment 2A. The compound of embodiment 1A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein L^2 is O, such that the compound is of formula (I-A):



(I-A),

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

[0493] Embodiment 3A. The compound of embodiment 1A or embodiment 2A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein *n* is 1, or 2.

[0494] Embodiment 4A. The compound of any one of embodiments 1A-3A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is H, C_{1-6}alkyl, C_{3-10}cycloalkyl, or 3-15 membered heterocyclyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more halo, -OH, $-NH_2$, or C_{1-6}alkoxy, and the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more -OH.

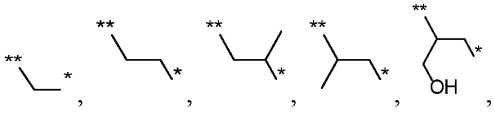
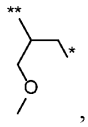
[0495] Embodiment 5A. The compound of any one of embodiments 1A-4A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein *m* is 0, 1, or 2.

[0496] Embodiment 6A. The compound of any one of embodiments 1A-5A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is halo, -CN, or -C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^1 is optionally substituted with one or more halo.

[0497] Embodiment 7A. The compound of any one of embodiments 1A-6A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein *p* is 0 or 1.

[0498] Embodiment 8A. The compound of any one of embodiments 1A-7A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^3 is C_{1-6}alkyl.

[0499] Embodiment 9A. The compound of any one of embodiments 1A-8A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein L^1 is C_{1-6}alkylene, wherein the C_{1-6}alkylene of L^1 is optionally substituted with one or more C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with -OH or C_{1-6}alkoxy.

[0500] Embodiment 10A. The compound of any one of embodiments 1A-9A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein L^1 is selected from the group consisting of  , and  , wherein, for each L^1, * denotes the point of attachment to L^2 and ** denotes the point of attachment to the remainder of the molecule.

[0501] Embodiment 11A. The compound of any one of embodiments 1A-10A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein L^2 is O.

[0502] Embodiment 12A. The compound of any one of embodiments 1A-11A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein L^3 is absent.

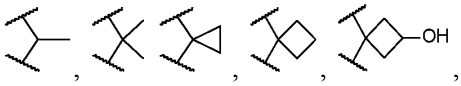
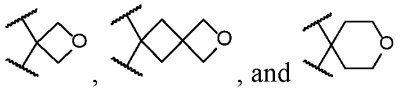
[0503] Embodiment 13A. The compound of any one of embodiments 1A-12A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein L^3 is -O-, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or C_{1-6}alkylene, wherein

the C_{1-6}alkylene of L^3 is optionally substituted with one or more C_{1-6}alkyl,

the C_{3-10}cycloalkyl membered heterocyclyl of L^3 is optionally substituted with one or more –OH, and

the 3-10 membered heterocyclyl of L^3 is optionally substituted with one or more –OH.

[0504] Embodiment 14A. The compound of any one of embodiments 1A-11A, and 13A or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing,

wherein L^3 is selected from the group consisting of -O-,  ,  , and .

[0505] Embodiment 15A. The compound of any one of embodiments 1A-14A or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^4 is $S(O)_2$-R^a, 5-10 membered heteroaryl, -$N(R^d)_2$, -NS(O)-(C_{1-3}alkyl)$_2$, -C(O)-$N(R^e)_2$, 3-6 membered heterocyclyl, -S(O)(N-C_{1-3}alkyl)-(C_{1-3}alkyl), or -CN, wherein

the 5-20 membered heteroaryl of R^4 is optionally substituted with one or more C_{1-6}alkyl, and

the 3-6 membered heterocyclyl optionally substituted with one or more oxo or C_{1-6}alkyl.

[0506] Embodiment 16A. The compound of embodiment 15A or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^a is C_{1-6}alkyl, is C_{3-10}cycloalkyl, or is 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^a is optionally substituted with one or more halo, -OH, $S(O)_2$-C_{1-6}alkyl, or -N(C_{1-6}alkyl)-C(O)-C_{1-6}alkyl,

the C_{3-10}cycloalkyl of R^a is optionally substituted with one or more -OH, $C(O)_2$-C_{1-6}alkyl, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, –C(O)-C_{3-10}heterocyclyl or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more -OH, and

the 3-10 membered heterocyclyl of R^a is optionally substituted with one or more C_{1-6}alkyl.

[0507] Embodiment 17A. The compound of embodiment 15A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein each of R^d is independently H, C_{1-6} alkyl, or -$S(O)_2$-R^a, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more -OH, and wherein R^a is C_{1-6}alkyl.

[0508] Embodiment 18A. The compound of embodiment 15A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein each of R^e is independently H, C_{1-6}alkyl, or 3-10 membered heterocycle, wherein the 3-6 membered heterocycle is optionally substituted with one or more oxo.

[0509] Embodiment 19A. The compound of embodiment 15A or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein both R^e together with the N to which they are attached are taken together to form a 3-10 membered heterocyclyl, wherein the 3-10 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, $-NH_2$, $-NH-S(O)_2-R^a$, or $-S(O)_2-R^a$, wherein R^a is C_{1-6}alkyl.

[0510] Embodiment 20A. The compound of any one of embodiments 1A-19A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein each of X^1 and X^2 is $C(R^5)$.

[0511] Embodiment 21A. The compound of any one of embodiments 1A-19A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein one of X^1 and X^2 is N and the other is $C(R^5)$.

[0512] Embodiment 22A. The compound of any one of embodiments 1A-19A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein one of X^1 and X^2 is CR^5, and the other of X^1 and X^2 is C that is taken together with R^4, and the atoms to which they are attached, to form a 5-10 membered heterocyclyl optionally substituted with one or more of R^b.

[0513] Embodiment 23A. The compound of embodiment 22A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^b is halo, oxo, C_{1-6}alkyl, $-C(O)-C_{1-6}$alkyl, $-C(O)-NH_2$, $-C(O)-NH(C_{1-6}$alkyl), $-C(O)-N(C_{1-6}$alkyl$)_2$, $-S(O)_2-R^a$, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, OH, or $-S(O)_2-C_{1-6}$alkyl, and the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more -OH.

[0514] Embodiment 24A. The compound of any one of embodiments 1A-19A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein one of X^1 and X^2 is CR^5, and the other of X^1 and X^2 is C that is taken together with R^4, and the atoms to which they are attached, to form a 5-10 membered heteroaryl optionally substituted with one or more R^c.

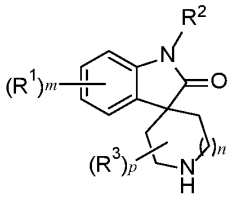
[0515] Embodiment 25A. The compound of embodiment 24A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein, R^c is halo, C_{1-6}alkyl, $-C(O)-C_{1-6}$alkyl, $-C(O)-NH_2$, $-C(O)-NH(C_{1-6}$alkyl), $-C(O)-N(C_{1-6}$alkyl$)_2$, $-S(O)_2-R^a$, C_{3-10}cycloalkyl,

and 3-10 membered heterocyclyl, wherein the C_{1-6}alkyl of R^c is optionally substituted with one or more -$S(O)_2$-C_{1-6}alkyl, and the C_{3-10}cycloalkyl of R^c is optionally substituted with one or more -OH.

[0516] Embodiment 26A. The compound of any one of embodiments 1A-25A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^5 is independently at each occurrence, H, halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH and wherein the C_{1-6}alkoxy is optionally substituted with one or more halo.

[0517] Embodiment 27A. The compound of embodiment 1A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, is selected from Compounds 1-273 of Table 1.

[0518] Embodiment 29A. A method for preparing a compound of embodiment 1A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, comprising a step of reacting a compound of formula I'-A:



(I'-A)

wherein:

m is an integer from 0 to 4;

n is an integer from 0 to 2;

p is an integer from 0 to 10;

R^1, if present is, independently at each occurrence selected from the group consisting of halo, -CN, C_{1-6}alkoxy or -C_{1-6}alkyl, wherein

the C_{1-6}alkoxy of R^1 is optionally substituted with one or more halo, and

the C_{1-6}alkyl of R^1 is optionally substituted with one or more halo;

R^2 is H, C_{1-6}alkyl, C_{3-10}cycloalkyl, or 3-15 membered heterocyclyl, wherein

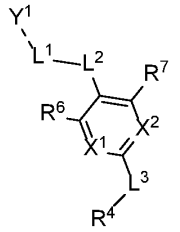
the C_{1-6}alkyl of R^2 is optionally substituted with one or more halo, -OH, -NH_2, or C_{1-6}alkoxy, and

the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more -OH; and

R^3, if present, is C_{1-6}alkyl;

with:

a compound of formula (I'-B):



(I'-B)

wherein:

the dashed line represents a single or double bond;

Y^1 is halo, oxo, or a sulfonate ester

L^1 is C_{1-6}alkylene, wherein the C_{1-6}alkylene of L^1 is optionally substituted with one or more C_{1-6}alkyl, and wherein the C_{1-6}alkyl is further optionally substituted with one or more -OH or C_{1-6}alkoxy;

L^2 is O or $N(R^x)$, wherein R^x is H or C_{1-6}alkyl; and

either

(1) L^3 is absent or is O, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or C_{1-6}alkylene, wherein the C_{1-6}alkylene of L^3 is optionally substituted with one or more C_{1-6}alkyl, and the 3-10 membered heterocyclyl is optionally substituted with one or more –OH;

X^1 and X^2 are each independently N or $C(R^5)$; and

R^4 is:

(i) $-S(O)_2-R^a$;

(ii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^4 is optionally substituted with one or more C_{1-6}alkyl;

(iii) $-N(R^d)_2$, wherein R^d is independently at each occurrence H, C_{1-6} alkyl, or $-S(O)_2-R^a$, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more –OH,

(iv) $-NS(O)-(C_{1-6}alkyl)_2$, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more –OH,

(v) -C(O)-N(R^e)$_2$ wherein R^e is independently at each occurrence H, C_{1-6} alkyl, or 3-10 membered heterocycle, wherein the 3-10 membered heterocycle is optionally substituted with one or more oxo, or both R^e together with the N to which they are attached are taken together to form a 3-10 membered heterocyclyl, wherein the 3-10 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, NH-S(O)$_2$-R^a, or -S(O)$_2$-R^a,

(vi) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl or oxo,

(vii) -S(O)-N(C_{1-6}alkyl)-(C_{1-6}alkyl),

(viii) –CN

or

(2) L^3 is absent; and

one of X^1 and X^2 is N or C(R^5); and

the other of X^1 and X^2 is N or C that is taken together with R^4, and the atoms to which they are attached, to form a 5-10 membered heterocyclyl or a 5-20 membered heteroaryl, wherein

the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is, independently at each occurrence, selected from the group consisting of halo, oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -S(O)$_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, OH, or -S(O)$_2$-C_{1-6}alkyl, and

the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more -OH, and

the 5-20 membered heteroaryl is optionally substituted with one or more R^c, wherein R^c is, independently at each occurrence, selected from the group consisting of halo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -S(O)$_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more -S(O)$_2$-C_{1-6}alkyl, and

the C_{3-10}cycloalkyl of R^c is optionally substituted with one or more -OH;

R^a is, independently at each occurrence:

(i) C_{1-6}alkyl optionally substituted with one or more halo, -OH, -$S(O)_2$-C_{1-6}alkyl, or -N(C_{1-6}alkyl)-C(O)-C_{1-6}alkyl, or

(ii) C_{3-10}cycloalkyl optionally substituted with one or more -OH, -$C(O)_2$-C_{1-6}alkyl, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, or –C(O)-C_{3-10}heterocyclyl, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more -OH, or

(iii) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl;

R^5 is, independently at each occurrence, H, halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH and wherein the C_{1-6}alkoxy is optionally substituted with one or more halo;

R^6 and R^7 are each independently H or halo;

to give a compound of embodiment 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0519] Embodiment 30A. The method of embodiment 29A, wherein the compound of embodiment 1 is prepared by a step comprising:

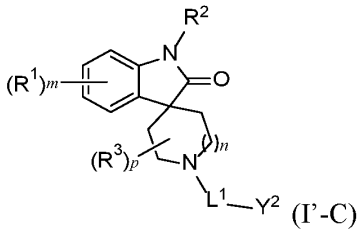
a) alkylation of an amine of formula (I'-A) with an alkyl halide, or sulfonate ester compound of formula (I'-B) in the presence of an inorganic base; or

b) reductive amination of a ketone of formula (I'-B) with an amine of formula (I'-A).

[0520] Embodiment 31A. The method of embodiment 30A, wherein the inorganic base is selected from the group consisting of potassium carbonate, and sodium bicarbonate.

[0521] Embodiment 32A. The method of embodiment 30A, wherein the reductive amination proceeds under the action of sodium triacetoxyborohydride, titanium tetraiopropoxide and acetic acid.

[0522] Embodiment 33A. A method for preparing a compound of embodiment 1A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, comprising a step of reacting a compound of formula I'-C:



(I'-C)

wherein:

m is an integer from 0 to 4;

n is an integer from 0 to 2;

p is an integer from 0 to 10;

R^1, if present is, independently at each occurrence selected from the group consisting of halo, -CN, C_{1-6}alkoxy or -C_{1-6}alkyl, wherein

the C_{1-6}alkoxy of R^1 is optionally substituted with one or more halo, and

the C_{1-6}alkyl of R^1 is optionally substituted with one or more halo;

R^2 is H, C_{1-6}alkyl, C_{3-10}cycloalkyl, or 3-15 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^2 is optionally substituted with one or more halo, -OH, -NH_2, or C_{1-6}alkoxy, and

the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more -OH;

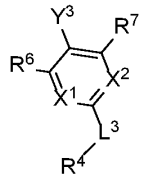
R^3, if present, is C_{1-6}alkyl;

L^1 is C_{1-6}alkylene, wherein the C_{1-6}alkylene of L^1 is optionally substituted with one or more C_{1-6}alkyl, and wherein the C_{1-6}alkyl is further optionally substituted with one or more -OH or C_{1-6}alkoxy; and

Y^2 is halo, –OH or NH_2;

with:

a compound of formula (I'-D):



(I'-D)

wherein:

Y^3 is –OH or NH(R^x), wherein R^x is H or C_{1-6}alkyl; and

either

(1) L^3 is absent or is O, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or C_{1-6}alkylene, wherein

the C_{1-6}alkylene of L^3 is optionally substituted with one or more C_{1-6}alkyl, and

the 3-10 membered heterocyclyl is optionally substituted with one or more –OH;

X^1 and X^2 are each independently N or $C(R^5)$; and

R^4 is:

(i) $-S(O)_2-R^a$;

(ii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^4 is optionally substituted with one or more C_{1-6}alkyl;

(iii) $-N(R^d)_2$, wherein R^d is independently at each occurrence H, C_{1-6} alkyl, or $-S(O)_2-R^a$, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more –OH,

(iv) $-NS(O)-(C_{1-6}alkyl)_2$, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more –OH,

(v) $-C(O)-N(R^e)_2$ wherein R^e is independently at each occurrence H, C_{1-6} alkyl, or 3-10 membered heterocycle, wherein the 3-10 membered heterocycle is optionally substituted with one or more oxo, or both R^e together with the N to which they are attached are taken together to form a 3-10 membered heterocyclyl, wherein the 3-10 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, $NH-S(O)_2-R^a$, or $-S(O)_2-R^a$,

(vi) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl or oxo,

(vii) $-S(O)-N(C_{1-6}alkyl)-(C_{1-6}alkyl)$,

(viii) –CN;

or

(2) L^3 is absent; and

one of X^1 and X^2 is N or $C(R^5)$; and

the other of X^1 and X^2 is N or C that is taken together with R^4, and the atoms to which they are attached, to form a 5-10 membered heterocyclyl or a 5-20 membered heteroaryl, wherein

the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is, independently at each occurrence, selected from the group consisting of halo, oxo, C_{1-6}alkyl, $-C(O)-C_{1-6}$alkyl, $-C(O)-NH_2$, $-C(O)-NH(C_{1-6}alkyl)$, $-C(O)-N(C_{1-6}alkyl)_2$, $-S(O)_2-R^a$, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, OH, or $-S(O)_2-C_{1-6}$alkyl, and

the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more -OH, and

the 5-20 membered heteroaryl is optionally substituted with one or more R^c, wherein

R^c is, independently at each occurrence, selected from the group consisting of halo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -S(O)$_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more -S(O)$_2$-C_{1-6}alkyl, and

the C_{3-10}cycloalkyl of R^c is optionally substituted with one or more -OH;

R^a is, independently at each occurrence:

(i) C_{1-6}alkyl optionally substituted with one or more halo, -OH, -S(O)$_2$-C_{1-6}alkyl, or -N(C_{1-6}alkyl)-C(O)-C_{1-6}alkyl, or

(ii) C_{3-10}cycloalkyl optionally substituted with one or more -OH, -C(O)$_2$-C_{1-6}alkyl, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, or –C(O)-C_{3-10}heterocyclyl, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more -OH, or

(iii) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl;

R^5 is, independently at each occurrence, H, halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH and wherein the C_{1-6}alkoxy is optionally substituted with one or more halo; and

R^6 and R^7 are each independently H or halo;

to give a compound of embodiment 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0523] Embodiment 34A. The method of embodiment 33A, wherein the compound of embodiment 1 is prepared by a step comprising:

a) coupling of an alcohol compound of formula (I'-C) with a phenol compound of formula (I'-D), or a heterocyclic variant, under Mitsunobu-type reaction conditions; or

b) reacting an alkyl halide compound of formula (I'-C) with a phenol or amine compound of formula (I'-D), in the presence of a catalyst.

[0524] Embodiment 35A. The method of embodiment 34A, wherein the Mitsunobi-type reaction conditions comprises coupling of an alcohol compound of formula (I'-C) with a phenol compound

of formula (I'-D), or a heterocyclic variant, in the presence of triphenylphosphine and diisopropyl azodicarboxylate.

[0525] Embodiment 36A. The method of embodiment 34A, wherein the catalyst is silver oxide or potassium carbonate.

[0526] Embodiment 37A. A pharmaceutical composition, comprising (i) a compound of any one of embodiments 1A-28A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) one or more pharmaceutically acceptable excipients.

[0527] Embodiment 38A. A method of modulating APOL1 in a cell, comprising exposing the cell to a composition comprising an effective amount of a compound of any one or embodiments 1A-28A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition of embodiment 37A.

[0528] Embodiment 39A. A method of inhibiting APOL1 in a cell, comprising exposing the cell to a composition comprising an effective amount of a compound of any one or embodiments 1A-28A or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition of embodiment 37A.

[0529] Embodiment 40A. A method of treating an APOL1-mediated disease, disorder, or condition in an individual in need thereof, comprising administering to the individual a compound of any one of embodiments 1A-28A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition of embodiment 37A.

[0530] Embodiment 41A. The method of embodiment 40A, 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.

[0531] Embodiment 42A. The method of embodiment 40A or embodiment 41A, wherein the disease, disorder, or condition is a kidney disease.

[0532] Embodiment 43A. The method of any one of embodiments 40A-42A, wherein the disease, disorder, or condition is a chronic kidney disease (CKD).

[0533] Embodiment 44A. A method of delaying the development of an APOL1-mediated disease, disorder, or condition, comprising administering a compound of any one of embodiments 1A-28A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition of embodiment 37A, to an individual who is at risk of developing an APOL1-mediated disease, disorder, or condition.

[0534] Embodiment 45A. The method of embodiment 44A, wherein the APOL1-mediated disease, disorder, or condition is a kidney disease.

[0535] Embodiment 46A. The method of embodiment 44A or embodiment 45A, wherein the APOL1-mediated disease, disorder, or condition is a chronic kidney disease.

[0536] Embodiment 47A. The method of embodiment 44A, wherein the APOL1-mediated 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.

[0537] Embodiment 48A. The method of any one of embodiments 40A-47A, wherein the individual has an APOL1 mutation.

[0538] Embodiment 49A. The method of embodiment 48A, wherein the APOL1 mutation is a gain-of-function mutation.

[0539] Embodiment 50A. The method of any one of embodiments 40A-49A, wherein a therapeutically effective amount of a compound of any one of embodiments 1A-28A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition of embodiment 37A, is administered.

[0540] Embodiment 51A. A kit, comprising (i) a compound of any one of embodiments 1A-28A, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition of embodiment 37A, and (ii) instructions for use in treating an APOL1-mediated disease, disorder, or condition in an individual in need thereof.

[0541] Embodiment 52A. The kit of embodiment 51A, wherein the disease, disorder, or condition is a kidney disease.

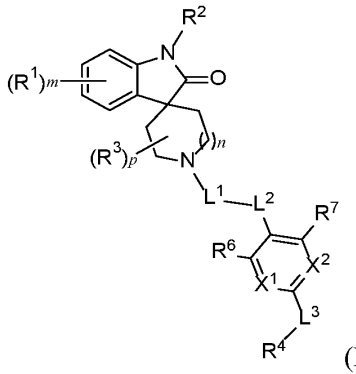
[0542] Embodiment 53A. The kit of embodiment 51A or embodiment 52A, wherein the disease, disorder, or condition is a chronic kidney disease (CKD).

[0543] Embodiment 54A. The kit of any one of embodiments 51A-53A, 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.

[0544] Embodiment 55A. The kit of any one of embodiments 51A-54A, wherein the individual has an APOL1 mutation.

[0545] Embodiment 56A. The kit of embodiment 55A, wherein the APOL1 mutation is a gain-of-function mutation.

[0546] Embodiment 1B. A compound of formula (I'):



(I'),

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

m is an integer from 0 to 4;

n is an integer from 0 to 2;

p is an integer from 0 to 10;

R^1, if present is, independently at each occurrence selected from the group consisting of halo, -CN, C_{1-6}alkoxy, or C_{1-6}alkyl, wherein

the C_{1-6}alkoxy of R^1 is optionally substituted with one or more halo, and

the C_{1-6}alkyl of R^1 is optionally substituted with one or more halo;

R^2 is H, C_{1-6}alkyl, C_{3-10}cycloalkyl, or 3-15 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^2 is optionally substituted with one or more halo, -OH, $-NH_2$, or C_{1-6}alkoxy, and

the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more -OH;

R^3, if present, is C_{1-6}alkyl;

L^1 is C_{1-6}alkylene, wherein the C_{1-6}alkylene of L^1 is optionally substituted with one or more C_{1-6}alkyl, and wherein the C_{1-6}alkyl is further optionally substituted with one or more -OH or C_{1-6}alkoxy;

L^2 is O or $N(R^x)$, wherein R^x is H or C_{1-6}alkyl; and

either

(1) L^3 is absent or is O, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or C_{1-6}alkylene, wherein

the C_{3-10}cycloalkyl is optionally substituted with one or more –OH, or C_{1-6}alkyl,

the C_{1-6}alkylene of L^3 is optionally substituted with one or more –OH, or C_{1-6}alkyl, and

the 3-10 membered heterocyclyl is optionally substituted with one or more –OH;

X^1 and X^2 are each independently N or $C(R^5)$; and

R^4 is:

(i) $-S(O)_2-R^a$;

(ii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^4 is optionally substituted with one or more C_{1-6}alkyl;

(iii) $-N(R^d)_2$, wherein R^d is independently at each occurrence H, C_{1-6} alkyl, or $-S(O)_2-R^a$, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more –OH,

(iv) $-NS(O)-(C_{1-6}alkyl)_2$, wherein the C_{1-6}alkyl is optionally substituted with one or more –OH,

(v) $-C(O)-N(R^e)_2$ wherein R^e is independently at each occurrence H, C_{1-6} alkyl, or 3-10 membered heterocycle, wherein the 3-10 membered heterocycle is optionally substituted with one or more oxo, or both R^e together with the N to which they are attached are taken together to form a 3-10 membered heterocyclyl, wherein the 3-10 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, $-NH-S(O)_2-R^a$, or $-S(O)_2-R^a$,

(vi) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl, -OH , oxo or $-S(O)_2R^a$,

(vii) $-S(O)-N(C_{1-6}alkyl)-(C_{1-6}alkyl)$,

(viii) -CN,

(ix) $-(CH_2)_qOH$, wherein q is an integer from 0-6,

(x) $-C(O)-C_{1-6}$alkyl, or

(xi) $-P(O)(C_{1-6}alkyl)_2$;

or

(2) L^3 is absent; and

one of X^1 and X^2 is N or $C(R^5)$; and

the other of X^1 and X^2 is N or C that is taken together with R^4, and the atoms to which they are attached, to form a 5-10 membered heterocyclyl or a 5-20 membered heteroaryl, wherein

the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is, independently at each occurrence, selected from the group consisting of halo, oxo, C_{1-6}alkyl, $-C(O)-C_{1-6}$alkyl, $-C(O)-NH_2$, $-C(O)-NH(C_{1-6}alkyl)$, $-C(O)-N(C_{1-6}alkyl)_2$, $-S(O)_2-R^a$, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, OH, $-S(O)_2-C_{1-6}$alkyl, or C_{3-10}cycloalkyl, and

wherein the C_{3-10}cycloalkyl of the C_{1-6}alkyl of R^b is further optionally substituted with one or more C_{1-6}alkyl or -OH and

the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more -OH, C_{3-10}cycloalkyl, or C_{1-6}alkyl, and

wherein the C_{1-6}alkyl of the C_{3-10}cycloalkyl of R^b is further optionally substituted with one or more –OH, and

the 5-20 membered heteroaryl is optionally substituted with one or more R^c, wherein R^c is, independently at each occurrence, selected from the group consisting of halo, C_{1-6}alkyl, $-C(O)-C_{1-6}$alkyl, $-C(O)-NH_2$, $-C(O)-NH(C_{1-6}alkyl)$, $-C(O)-N(C_{1-6}alkyl)_2$, $-S(O)_2-R^a$, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more $-S(O)_2-C_{1-6}$alkyl,

the C_{3-10}cycloalkyl of R^c is optionally substituted with one or more –OH, or C_{1-6}alkyl,

and the 3-10 membered heterocyclyl of R^c is optionally substituted with one or more -OH, or C_{1-6}alkyl, and

wherein the C_{1-6}alkyl of 3-10 membered heterocyclyl of R^c is further optionally substituted with one or more -OH;

R^a is, independently at each occurrence:

(i) C_{1-6}alkyl optionally substituted with one or more halo, -OH, -$S(O)_2$-C_{1-6}alkyl, or -$N(C_{1-6}alkyl)$-C(O)-C_{1-6}alkyl,

(ii) C_{3-10}cycloalkyl optionally substituted with one or more -OH, -$C(O)_2$-C_{1-6}alkyl, -C(O)-$NH(C_{1-6}alkyl)$, -C(O)-$N(C_{1-6}alkyl)_2$, or –C(O)-C_{3-10}heterocyclyl, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more -OH, or

(iii) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl;

R^5 is, independently at each occurrence, H, halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH and wherein the C_{1-6}alkoxy of R^5 is optionally substituted with one or more halo; and

R^6 and R^7 are each independently H or halo.

[0547] Embodiment 15B. The compound of embodiments 1B or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^4 is $S(O)_2$-R^a, 5-10 membered heteroaryl, -$N(R^d)_2$, -NS(O)-$(C_{1-3}alkyl)_2$, -C(O)-$N(R^e)_2$, 3-6 membered heterocyclyl, -S(O)(N-C_{1-3}alkyl)-(C_{1-3}alkyl), –CN, or -OH, wherein

the 5-20 membered heteroaryl of R^4 is optionally substituted with one or more C_{1-6}alkyl, and

the 3-6 membered heterocyclyl optionally substituted with one or more oxo or C_{1-6}alkyl.

[0548] Embodiment 23B. The compound of embodiment 1B, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein one of X^1 and X^2 is CR^5, and the other of X^1 and X^2 is C that is taken together with R^4, and the atoms to which they are attached, to form a 5-10 membered heterocyclyl optionally substituted with one or more of R^b.

[0549] Embodiments 24B. The compound of embodiment 23B, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^b is halo,

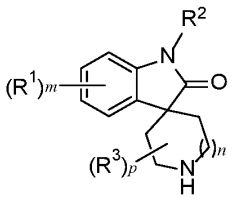
oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -S(O)$_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, OH, or -S(O)$_2$-C_{1-6}alkyl, and the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more -OH, C_{3-10}cycloalkyl, or C_{1-6}alkyl.

[0550] Embodiments 25B. The compound of embodiment 24B, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein, R^c is halo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -S(O)$_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein the C_{1-6}alkyl of R^c is optionally substituted with one or more -S(O)$_2$-C_{1-6}alkyl, and the C_{3-10}cycloalkyl of R^c is optionally substituted with one or more -OH, or C_{1-6}alkyl.

METHODS OF PREPARING

[0551] The present disclosure further provides methods for preparing the compounds of present invention. In some aspect, provided herein are methods of preparing a compound of formula (II), or any embodiment or variation thereof, such as a compound of formula (I'), (I), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), or (II-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0552] In some embodiments, a method for preparing a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, comprises a step of reacting a compound of formula I'-A:



(I'-A)

wherein:

m is an integer from 0 to 4;

n is an integer from 0 to 2;

p is an integer from 0 to 10;

R^1, if present is, independently at each occurrence selected from the group consisting of halo, -CN, C_{1-6}alkoxy, or -C_{1-6}alkyl, wherein

the C_{1-6}alkoxy of R^1 is optionally substituted with one or more halo, and

the C_{1-6}alkyl of R^1 is optionally substituted with one or more halo;

R^2 is H, C_{1-6}alkyl, C_{3-10}cycloalkyl, or 3-15 membered heterocyclyl, wherein

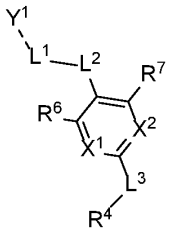
the C_{1-6}alkyl of R^2 is optionally substituted with one or more halo, -OH, -NH_2, or C_{1-6}alkoxy, and

the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more -OH; and

R^3, if present, is C_{1-6}alkyl;

with:

a compound of formula (I'-B):



(I'-B)

wherein:

the dashed line represents a single or double bond;

Y^1 is halo, oxo, or a sulfonate ester

L^1 is C_{1-6}alkylene, wherein the C_{1-6}alkylene of L^1 is optionally substituted with one or more C_{1-6}alkyl, and wherein the C_{1-6}alkyl is further optionally substituted with one or more -OH or C_{1-6}alkoxy;

L^2 is O or N(R^x), wherein R^x is H or C_{1-6}alkyl; and

either

(1) L^3 is absent or is O, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or C_{1-6}alkylene, wherein

the C_{1-6}alkylene of L^3 is optionally substituted with one or more C_{1-6}alkyl, and

the 3-10 membered heterocyclyl is optionally substituted with one or more –OH;

X^1 and X^2 are each independently N or C(R^5); and

R^4 is:

(i) $-S(O)_2-R^a$,

(ii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^4 is optionally substituted with one or more C_{1-6}alkyl,

(iii) $-N(R^d)_2$, wherein R^d is independently at each occurrence H, C_{1-6} alkyl, or $-S(O)_2-R^a$, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more –OH,

(iv) $-NS(O)-(C_{1-6}alkyl)_2$, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more –OH,

(v) $-C(O)-N(R^e)_2$ wherein R^e is independently at each occurrence H, C_{1-6} alkyl, or 3-10 membered heterocycle, wherein the 3-10 membered heterocycle is optionally substituted with one or more oxo, or both R^e together with the N to which they are attached are taken together to form a 3-10 membered heterocyclyl, wherein the 3-10 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, $NH-S(O)_2-R^a$, or $-S(O)_2-R^a$,

(vi) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl or oxo,

(vii) $-S(O)-N(C_{1-6}alkyl)-(C_{1-6}alkyl)$, or

(viii) -CN;

or

(2) L^3 is absent; and

one of X^1 and X^2 is N or $C(R^5)$; and

the other of X^1 and X^2 is N or C that is taken together with R^4, and the atoms to which they are attached, to form a 5-10 membered heterocyclyl or a 5-20 membered heteroaryl, wherein

the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is, independently at each occurrence, selected from the group consisting of halo, oxo, C_{1-6}alkyl, $-C(O)-C_{1-6}$alkyl, $-C(O)-NH_2$, $-C(O)-NH(C_{1-6}alkyl)$, $-C(O)-N(C_{1-6}alkyl)_2$, $-S(O)_2-R^a$, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, OH, or $-S(O)_2-C_{1-6}$alkyl, and

the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more -OH, and

the 5-20 membered heteroaryl is optionally substituted with one or more R^c, wherein R^c is, independently at each occurrence, selected from the group consisting of halo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -S(O)$_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more -S(O)$_2$-C_{1-6}alkyl, and

the C_{3-10}cycloalkyl of R^c is optionally substituted with one or more -OH;

R^a is, independently at each occurrence:

(i) C_{1-6}alkyl optionally substituted with one or more halo, -OH, -S(O)$_2$-C_{1-6}alkyl, or -N(C_{1-6}alkyl)-C(O)-C_{1-6}alkyl, or

(ii) C_{3-10}cycloalkyl optionally substituted with one or more -OH, -C(O)$_2$-C_{1-6}alkyl, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, or –C(O)-C_{3-10}heterocyclyl, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more -OH, or

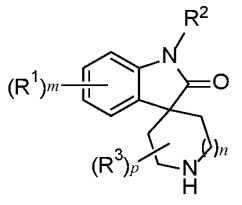
(iii) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl;

R^5 is, independently at each occurrence, H, halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH and wherein the C_{1-6}alkoxy is optionally substituted with one or more halo;

R^6 and R^7 are each independently H or halo;

to give a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0553] In some embodiments, a method for preparing a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, comprises a step of reacting a compound of formula I'-A':



(I'-A')

wherein:

m is an integer from 0 to 4;

n is an integer from 0 to 2;

p is an integer from 0 to 10;

R^1, if present is, independently at each occurrence selected from the group consisting of halo, -CN, C_{1-6}alkoxy, or -C_{1-6}alkyl, wherein

the C_{1-6}alkoxy of R^1 is optionally substituted with one or more halo, and

the C_{1-6}alkyl of R^1 is optionally substituted with one or more halo;

R^2 is H, C_{1-6}alkyl, C_{3-10}cycloalkyl, or 3-15 membered heterocyclyl, wherein

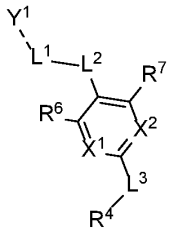
the C_{1-6}alkyl of R^2 is optionally substituted with one or more halo, -OH, -NH_2, or C_{1-6}alkoxy, and

the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more -OH; and

R^3, if present, is C_{1-6}alkyl;

with:

a compound of formula (I'-B'):



(I'-B')

wherein:

the dashed line represents a single or double bond;

Y^1 is halo, oxo, or a sulfonate ester

L^1 is C_{1-6}alkylene, wherein the C_{1-6}alkylene of L^1 is optionally substituted with one or more C_{1-6}alkyl, and wherein the C_{1-6}alkyl is further optionally substituted with one or more -OH or C_{1-6}alkoxy;

L^2 is O or N(R^x), wherein R^x is H or C_{1-6}alkyl; and

either

(1) L^3 is absent or is O, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or C_{1-6}alkylene, wherein

the C_{3-10}cycloalkyl is optionally substituted with one or more –OH, or C_{1-6}alkyl,

the C_{1-6}alkylene of L^3 is optionally substituted with one or more –OH, or C_{1-6}alkyl, and

the 3-10 membered heterocyclyl is optionally substituted with one or more –OH;

X^1 and X^2 are each independently N or $C(R^5)$; and

R^4 is:

(i) $-S(O)_2-R^a$;

(ii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^4 is optionally substituted with one or more C_{1-6}alkyl;

(iii) $-N(R^d)_2$, wherein R^d is independently at each occurrence H, C_{1-6} alkyl, or $-S(O)_2-R^a$, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more –OH,

(iv) $-NS(O)-(C_{1-6}alkyl)_2$, wherein the C_{1-6}alkyl is optionally substituted with one or more –OH,

(v) $-C(O)-N(R^e)_2$ wherein R^e is independently at each occurrence H, C_{1-6} alkyl, or 3-10 membered heterocycle, wherein the 3-10 membered heterocycle is optionally substituted with one or more oxo, or both R^e together with the N to which they are attached are taken together to form a 3-10 membered heterocyclyl, wherein the 3-10 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, $-NH-S(O)_2-R^a$, or $-S(O)_2-R^a$,

(vi) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl, -OH , oxo or $-S(O)_2R^a$,

(vii) $-S(O)-N(C_{1-6}alkyl)-(C_{1-6}alkyl)$,

(viii) -CN,

(ix) $-(CH_2)_qOH$, wherein q is an integer from 0-6,

(x) $-C(O)-C_{1-6}$alkyl, or

(xi) $-P(O)(C_{1-6}alkyl)_2$;

or

(2) L^3 is absent; and

one of X^1 and X^2 is N or $C(R^5)$; and

the other of X^1 and X^2 is N or C that is taken together with R^4, and the atoms to which they are attached, to form a 5-10 membered heterocyclyl or a 5-20 membered heteroaryl, wherein

the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is, independently at each occurrence, selected from the group consisting of halo, oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -S(O)$_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, OH, -S(O)$_2$-C_{1-6}alkyl, or C_{3-10}cycloalkyl, and

wherein the C_{3-10}cycloalkyl of the C_{1-6}alkyl of R^b is further optionally substituted with one or more C_{1-6}alkyl or -OH and

the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more -OH, C_{3-10}cycloalkyl, or C_{1-6}alkyl, and

wherein the C_{1-6}alkyl of the C_{3-10}cycloalkyl of R^b is further optionally substituted with one or more –OH, and

the 5-20 membered heteroaryl is optionally substituted with one or more R^c, wherein R^c is, independently at each occurrence, selected from the group consisting of halo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -S(O)$_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more -S(O)$_2$-C_{1-6}alkyl,

the C_{3-10}cycloalkyl of R^c is optionally substituted with one or more –OH, or C_{1-6}alkyl,

and the 3-10 membered heterocyclyl of R^c is optionally substituted with one or more -OH, or C_{1-6}alkyl, and

wherein the C_{1-6}alkyl of the 3-10 membered heterocyclyl of R^c is further optionally substituted with one or more -OH;

R^a is, independently at each occurrence:

(i) C_{1-6}alkyl optionally substituted with one or more halo, -OH, -S(O)$_2$-C_{1-6}alkyl, or -N(C_{1-6}alkyl)-C(O)-C_{1-6}alkyl,

(ii) C_{3-10}cycloalkyl optionally substituted with one or more -OH, -C(O)$_2$-C_{1-6}alkyl, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, or –C(O)-C_{3-10}heterocyclyl, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more -OH, or

(iii) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl;

R^5 is, independently at each occurrence, H, halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH and wherein the C_{1-6}alkoxy of R^5 is optionally substituted with one or more halo; and

R^6 and R^7 are each independently H or halo;

to give a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0554] In some embodiments, the compound of formula (I) is prepared by a step comprising:

a) alkylation of an amine of formula (I'-A) with an alkyl halide, or sulfonate ester compound of formula (I'-B) in the presence of an inorganic base; or

b) reductive amination of a ketone of formula (I'-B) with an amine of formula (I'-A).

[0555] In some embodiments, the compound of formula (I') is prepared by a step comprising:

a) alkylation of an amine of formula (I'-A') with an alkyl halide, or sulfonate ester compound of formula (I'-B') in the presence of an inorganic base; or

b) reductive amination of a ketone of formula (I'-B') with an amine of formula (I'-A').

[0556] In some embodiments, the compound of formula (I) is prepared by a step comprising alkylation of an amine of formula (I'-A) with an alkyl halide, or sulfonate ester compound of formula (I'-B) in the presence of an inorganic base. In some embodiments, the inorganic base is selected from the group consisting of potassium carbonate, and sodium bicarbonate.

[0557] In some embodiments, the compound of formula (I') is prepared by a step comprising alkylation of an amine of formula (I'-A') with an alkyl halide, or sulfonate ester compound of formula (I'-B') in the presence of an inorganic base. In some embodiments, the inorganic base is selected from the group consisting of potassium carbonate, and sodium bicarbonate.

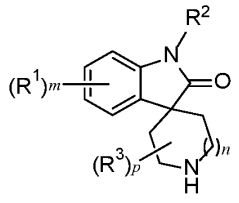
[0558] In some embodiments, the sulfonate ester compound of formula (I'-B) is a mesylate or a tosylate. In some embodiments, the sulfonate ester compound of formula (I'-B) is a mesylate, or CH_3SO_3-. In some embodiments, the sulfonate ester compound of formual (I'-B) is a tosylate or $CH_3C_6H_4SO_3$-.

[0559] In some embodiments, the sulfonate ester compound of formula (I'-B') is a mesylate or a tosylate. In some embodiments, the sulfonate ester compound of formula (I'-B') is a mesylate, or CH_3SO_3-. In some embodiments, the sulfonate ester compound of formual (I'-B') is a tosylate or $CH_3C_6H_4SO_3$-.

[0560] In some embodiments, the compound of formula (I) is prepared by a step comprising reductive amination of a ketone of formula (I'-B) with an amine of formula (I'-A). In some embodiments, the reductive amination proceeds under the action of sodium triacetoxyborohydride, titanium tetraiopropoxide and acetic acid.

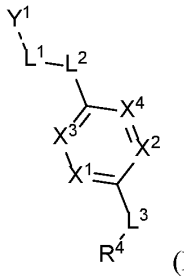
[0561] In some embodiments, the compound of formula (I') is prepared by a step comprising reductive amination of a ketone of formula (I'-B') with an amine of formula (I'-A'). In some embodiments, the reductive amination proceeds under the action of sodium triacetoxyborohydride, titanium tetraiopropoxide and acetic acid.

[0562] It is understood that the present disclosure also provides for methods of preparing compounds of formula (II). For example, compounds of formula (II) may be prepared by reacting a compound of formula (II'-A):



(II'-A),

wherein and *m*, *n*, *p*, R^1, and R^2 are as defined for a compound of formula (II), with a compound of formula (II'-B):

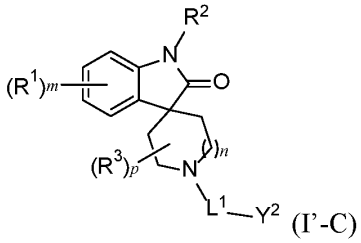


(II'-B),

wherein Y^1 is halo, oxo, or a sulfonate ester; and L^1, L^2, L^3, R^4, X^1, X^2, X^3, and X^4 are as defined for a compound of formula (II),

to give a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0563] In some embodiments, a method for preparing a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, comprises a step of reacting a compound of formula (I'-C):



(I'-C)

wherein:

m is an integer from 0 to 4;

n is an integer from 0 to 2;

p is an integer from 0 to 10;

R^1, if present is, independently at each occurrence selected from the group consisting of halo, -CN, C_{1-6}alkoxy, or -C_{1-6}alkyl, wherein

the C_{1-6}alkoxy of R^1 is optionally substituted with one or more halo, and

the C_{1-6}alkyl of R^1 is optionally substituted with one or more halo;

R^2 is H, C_{1-6}alkyl, C_{3-10}cycloalkyl, or 3-15 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^2 is optionally substituted with one or more halo, -OH, $-NH_2$, or C_{1-6}alkoxy, and

the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more -OH;

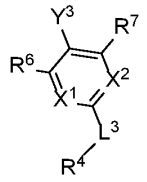
R^3, if present, is C_{1-6}alkyl;

L^1 is C_{1-6}alkylene, wherein the C_{1-6}alkylene of L^1 is optionally substituted with one or more C_{1-6}alkyl, and wherein the C_{1-6}alkyl is further optionally substituted with one or more -OH or C_{1-6}alkoxy; and

Y^2 is halo, -OH or $-NH_2$;

with:

a compound of formula (I'-D):



(I'-D)

wherein:

Y^3 is -OH or -NH(R^x), wherein each R^x is independently H or C_{1-6}alkyl; and

either

(1) L^3 is absent or is O, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or C_{1-6}alkylene, wherein the C_{1-6}alkylene of L^3 is optionally substituted with one or more C_{1-6}alkyl, and the 3-10 membered heterocyclyl is optionally substituted with one or more –OH;

X^1 and X^2 are each independently N or C(R^5); and

R^4 is:

(i) -S(O)$_2$-R^a;

(ii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^4 is optionally substituted with one or more C_{1-6}alkyl;

(iii) N(R^d)$_2$, wherein R^d is independently at each occurrence H, C_{1-6} alkyl, or -S(O)$_2$-R^a, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more –OH,

(iv) -NS(O)-(C_{1-6}alkyl)$_2$, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more –OH,

(v) -C(O)-N(R^e)$_2$ wherein R^e is independently at each occurrence H, C_{1-6} alkyl, or 3-10 membered heterocycle, wherein the 3-10 membered heterocycle is optionally substituted with one or more oxo, or both R^e together with the N to which they are attached are taken together to form a 3-10 membered heterocyclyl, wherein the 3-10 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, NH-S(O)$_2$-R^a, or -S(O)$_2$-R^a,

(vi) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl or oxo,

(vii) -S(O)-N(C_{1-6}alkyl)-(C_{1-6}alkyl),

(viii) -CN;

or

(2) L^3 is absent; and

one of X^1 and X^2 is N or $C(R^5)$; and

the other of X^1 and X^2 is N or C that is taken together with R^4, and the atoms to which they are attached, to form a 5-10 membered heterocyclyl or a 5-20 membered heteroaryl, wherein

the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is, independently at each occurrence, selected from the group consisting of halo, oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -$S(O)_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, OH, or -$S(O)_2$-C_{1-6}alkyl, and

the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more -OH, and

the 5-20 membered heteroaryl is optionally substituted with one or more R^c, wherein R^c is, independently at each occurrence, selected from the group consisting of halo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -$S(O)_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more -$S(O)_2$-C_{1-6}alkyl, and

the C_{3-10}cycloalkyl of R^c is optionally substituted with one or more -OH;

R^a is, independently at each occurrence:

(i) C_{1-6}alkyl optionally substituted with one or more halo, -OH, -$S(O)_2$-C_{1-6}alkyl, or -N(C_{1-6}alkyl)-C(O)-C_{1-6}alkyl, or

(ii) C_{3-10}cycloalkyl optionally substituted with one or more -OH, -$C(O)_2$-C_{1-6}alkyl, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, or –C(O)-C_{3-10}heterocyclyl, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more -OH, or

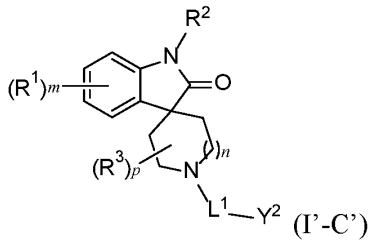
(iii) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl;

R^5 is, independently at each occurrence, H, halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH and wherein the C_{1-6}alkoxy is optionally substituted with one or more halo; and

R^6 and R^7 are each independently H or halo;

to give a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0564] In some embodiments, a method for preparing a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, comprises a step of reacting a compound of formula (I'-C'):



(I'-C')

wherein:

m is an integer from 0 to 4;

n is an integer from 0 to 2;

p is an integer from 0 to 10;

R^1, if present is, independently at each occurrence selected from the group consisting of halo, -CN, C_{1-6}alkoxy, or -C_{1-6}alkyl, wherein

the C_{1-6}alkoxy of R^1 is optionally substituted with one or more halo, and

the C_{1-6}alkyl of R^1 is optionally substituted with one or more halo;

R^2 is H, C_{1-6}alkyl, C_{3-10}cycloalkyl, or 3-15 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^2 is optionally substituted with one or more halo, -OH, $-NH_2$, or C_{1-6}alkoxy, and

the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more -OH;

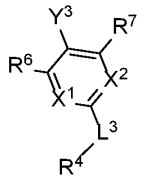
R^3, if present, is C_{1-6}alkyl;

L^1 is C_{1-6}alkylene, wherein the C_{1-6}alkylene of L^1 is optionally substituted with one or more C_{1-6}alkyl, and wherein the C_{1-6}alkyl is further optionally substituted with one or more -OH or C_{1-6}alkoxy; and

Y^2 is halo, -OH or $-NH_2$;

with:

a compound of formula (I'-D'):



(I'-D')

wherein:

Y^3 is –OH or NH(R^x), wherein each R^x is independently H or C_{1-6}alkyl; and

either

(1) L^3 is absent or is O, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or C_{1-6}alkylene, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more –OH, or C_{1-6}alkyl, the C_{1-6}alkylene of L^3 is optionally substituted with one or more –OH, or C_{1-6}alkyl, and the 3-10 membered heterocyclyl is optionally substituted with one or more –OH;

X^1 and X^2 are each independently N or C(R^5); and

R^4 is:

(i) -S(O)$_2$-R^a;

(ii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^4 is optionally substituted with one or more C_{1-6}alkyl;

(iii) -N(R^d)$_2$, wherein R^d is independently at each occurrence H, C_{1-6} alkyl, or -S(O)$_2$-R^a, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more –OH,

(iv) -NS(O)-(C_{1-6}alkyl)$_2$, wherein the C_{1-6}alkyl is optionally substituted with one or more –OH,

(v) -C(O)-N(R^e)$_2$ wherein R^e is independently at each occurrence H, C_{1-6} alkyl, or 3-10 membered heterocycle, wherein the 3-10 membered heterocycle is optionally substituted with one or more oxo, or both R^e together with the N to which they are attached are taken together to form a 3-10 membered heterocyclyl, wherein the 3-10 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, -NH-S(O)$_2$-R^a, or -S(O)$_2$-R^a,

(vi) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl, -OH , oxo or -S(O)$_2$$R^a$,

(vii) -S(O)-N(C_{1-6}alkyl)-(C_{1-6}alkyl),

(viii) -CN;

(ix) -$(CH_2)_q$OH, wherein q is an integer from 0-6; or

(x) -C(O)-C_{1-6}alkyl

(xi) -P(O)(C_{1-6}alkyl)$_2$

or

(2) L^3 is absent; and

one of X^1 and X^2 is N or C(R^5); and

the other of X^1 and X^2 is N or C that is taken together with R^4, and the atoms to which they are attached, to form a 5-10 membered heterocyclyl or a 5-20 membered heteroaryl, wherein

the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is, independently at each occurrence, selected from the group consisting of halo, oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -S(O)$_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, OH, -S(O)$_2$-C_{1-6}alkyl, or C_{3-10}cycloalkyl, and

wherein the C_{3-10}cycloalkyl of the C_{1-6}alkyl of R^b is further optionally substituted with one or more C_{1-6}alkyl or -OH and

the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more -OH, C_{3-10}cycloalkyl, or C_{1-6}alkyl, and

wherein the C_{1-6}alkyl of the C_{3-10}cycloalkyl of R^b is further optionally substituted with one or more –OH, and

the 5-20 membered heteroaryl is optionally substituted with one or more R^c, wherein R^c is, independently at each occurrence, selected from the group consisting of halo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -S(O)$_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more -S(O)$_2$-C_{1-6}alkyl,

the C_{3-10}cycloalkyl of R^c is optionally substituted with one or more –OH, or C_{1-6}alkyl,

and the 3-10 membered heterocyclyl of R^c is optionally substituted with one or more -OH, or C_{1-6}alkyl, and

wherein the C_{1-6}alkyl of the 3-10 membered heterocyclyl of R^c is further optionally substituted with one or more -OH;

R^a is, independently at each occurrence:

(i) C_{1-6}alkyl optionally substituted with one or more halo, -OH, -$S(O)_2$-C_{1-6}alkyl, or -N(C_{1-6}alkyl)-C(O)-C_{1-6}alkyl,

(ii) C_{3-10}cycloalkyl optionally substituted with one or more -OH, -$C(O)_2$-C_{1-6}alkyl, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, or –C(O)-C_{3-10}heterocyclyl, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more -OH, or

(iii) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl;

R^5 is, independently at each occurrence, H, halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH and wherein the C_{1-6}alkoxy of R^5 is optionally substituted with one or more halo; and

R^6 and R^7 are each independently H or halo;

to give a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0565] In some embodiments, the compound of formula (I) is prepared by a step comprising:

a) coupling of an alcohol compound of formula (I'-C) with a phenol compound of formula (I'-D), or a heterocyclic variant, under Mitsunobu-type reaction conditions; or

b) reacting an alkyl halide compound of formula (I'-C) with a phenol or amine compound of formula (I'-D), in the presence of a catalyst.

[0566] In some embodiments, the compound of formula (I') is prepared by a step comprising:

a) coupling of an alcohol compound of formula (I'-C') with a phenol compound of formula (I'-D'), or a heterocyclic variant, under Mitsunobu-type reaction conditions; or

b) reacting an alkyl halide compound of formula (I'-C') with a phenol or amine compound of formula (I'-D'), in the presence of a catalyst.

[0567] In some embodiments, the compound of formula (I) is prepared by a step comprising coupling of an alcohol compound of formula (I'-C) with a phenol compound of formula (I'-D), or a heterocyclic variant, under Mitsunobu-type reaction conditions. In some embodiments, the

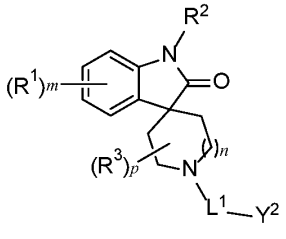
Mitsunobu-type reaction conditions comprises coupling of an alcohol compound of formula (I'-C) with a phenol compound of formula (I'-D), or a heterocyclic variant, in the presence of triphenylphosphine and diisopropyl azodicarboxylate.

[0568] In some embodiments, the compound of formula (I') is prepared by a step comprising coupling of an alcohol compound of formula (I'-C') with a phenol compound of formula (I'-D'), or a heterocyclic variant, under Mitsunobu-type reaction conditions. In some embodiments, the Mitsunobu-type reaction conditions comprises coupling of an alcohol compound of formula (I'-C') with a phenol compound of formula (I'-D'), or a heterocyclic variant, in the presence of triphenylphosphine and diisopropyl azodicarboxylate.

[0569] In some embodiments, the compound of formula (I) is prepared by a step comprising reacting an alkyl halide compound of formula (I'-C) with a phenol compound of formula (I'-D), in the presence of a base. In some embodiments, the base is silver oxide or potassium carbonate.

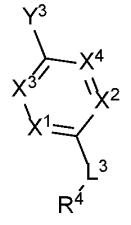
[0570] In some embodiments, the compound of formula (I') is prepared by a step comprising reacting an alkyl halide compound of formula (I'-C') with a phenol compound of formula (I'-D'), in the presence of a base. In some embodiments, the base is silver oxide or potassium carbonate.

[0571] It is understood that the present disclosure also provides for methods of preparing compounds of formula (II). For example, compounds of formula (II) may be prepared by reacting a compound of formula (II'-C):



(II'-C),

wherein Y^2 is halo, -OH or $-NH_2$; and *m*, *n*, *p*, R^1, R^2, R^3, and L^1 are as defined for a compound of formula (II), with a compound of formula (II'-D):



(II'-D),

wherein Y^3 is -OH or -NH(R^x), wherein each R^x is independently H or C_{1-6}alkyl; L^3, R^4, X^1, X^2, X^3, and X^4 are as defined for a compound of formula (II),

to give a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0572] In further examples, the compound of formula (II), formula (I'), formula (I), or any embodiment or variation thereof, such as a compound of formula (I), (I-A) (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), or (II-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing is prepared by methods shown in the examples below.

EXAMPLES

[0573] The following synthetic reaction schemes, which are detailed in the Schemes, General Procedures, and Examples, are merely illustrative of some of the methods by which the compounds of the present disclosure, or an embodiment or aspect thereof, can be synthesized. Various modifications to these synthetic reaction schemes can be made, as will be apparent to those of ordinary skill in the art.

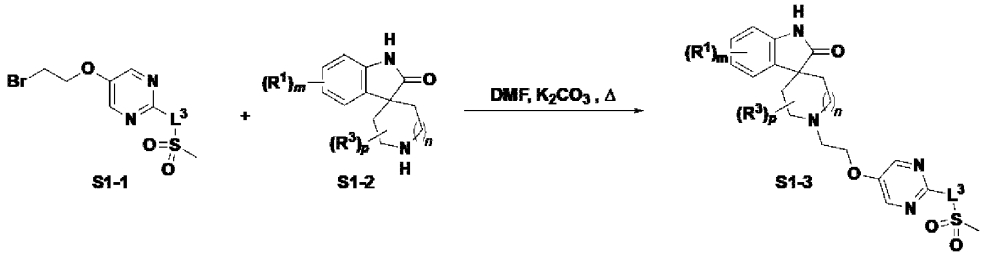
[0574] The starting materials and the intermediates of the synthetic reaction schemes can be isolated and purified if desired using conventional techniques, including but not limited to, filtration, distillation, crystallization, chromatography, and the like. Such materials can be characterized using conventional means, including physical constants and spectral data.

[0575] Although certain exemplary embodiments are depicted and described herein, the compounds of the present disclosure, or any variation or embodiment thereof, may be prepared using appropriate starting materials according to the methods described generally herein and/or by methods available to one of ordinary skill in the art.

Synthetic Examples

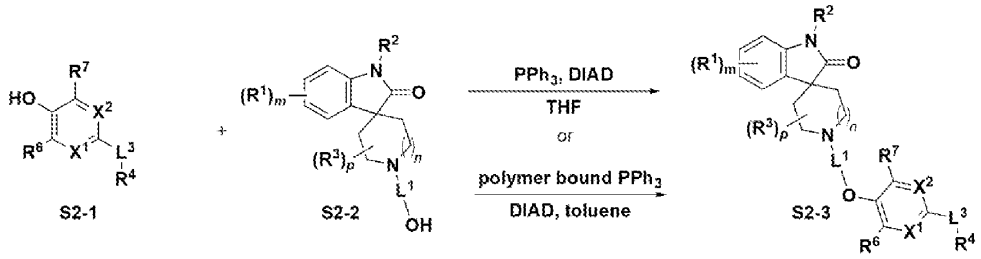
[0576] As depicted in the Schemes, General Procedures, and Examples below, in certain exemplary embodiments, compounds of formula (I), formula (I'), formula (II), or any variation or embodiment thereof, as described elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, are prepared according to the general procedures. The general methods below, and other methods known to synthetic chemists of ordinary skill in the art, can be applied to all formulae, variations, embodiments, and species described herein.

Scheme 1



[0577] Compounds of formula **S1-3** may be prepared according to **Scheme 1**. Alkylation of amine **S1-2** with an alkyl halide such as **S1-1** in the presence of an inorganic base such as potassium carbonate and a polar aprotic solvent such as DMF provides compound **S1-3**. In cases where L3 represents a chiral atom, compound **S1-3** may be further purified by chiral SFC to deliver single stereoisomers.

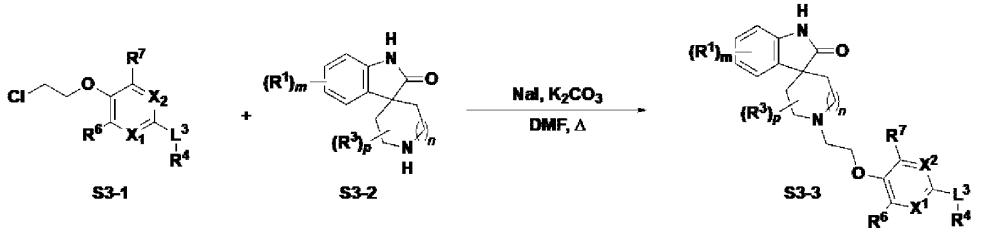
Scheme 2



[0578] Compounds of formula **S2-3** may be prepared may also be prepared by coupling a phenol or heterocyclic variant such as **S2-1** with an alcohol such as **S2-2** in the presence of triphenylphosphine and DIAD in an aprotic solvent such as THF, as depicted in **Scheme 2**.

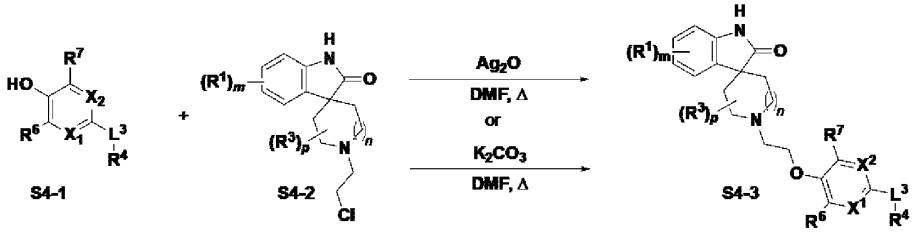
Alternative Mitsunobu-type reaction conditions with polymer-bound triphenylphosphine and DIAD in toluene may also be used to generate compounds of formula **S2-3**.

Scheme 3



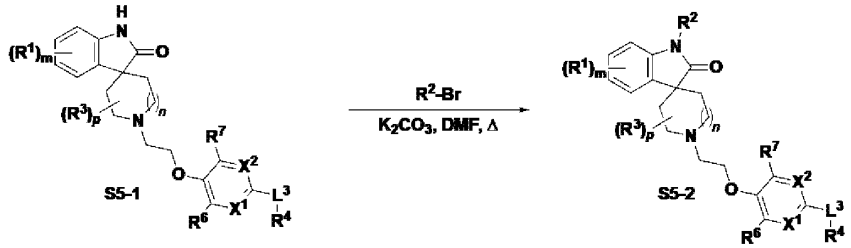
[0579] As outlined in **Scheme 3**, compounds of formula **S3-3** may be prepared from alkyl chlorides such as **S3-1** and amine **S3-2** by heating in an aprotic solvent such as DMF in the presence of sodium iodide and an inorganic base such as potassium carbonate.

Scheme 4



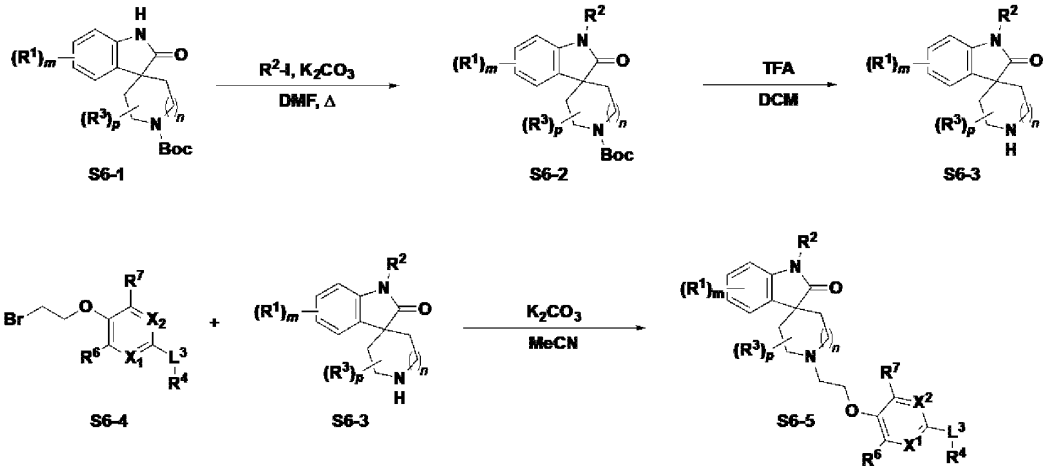
[0580] Compounds of formula **S4-3** may also be prepared from phenol **S4-1** and alkyl halide **S4-2** by heating in an aprotic solvent such as DMF in the presence of silver oxide, as shown in Scheme 4. Alternative reaction conditions involving potassium carbonate in DMF may also be used to generate compounds of formula **S4-3**.

Scheme 5



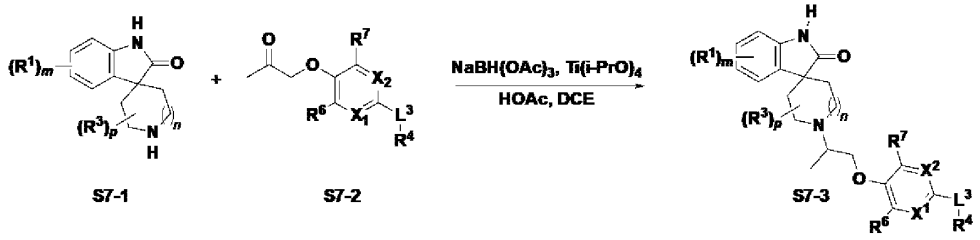
[0581] Oxindoles such as **S5-1** may be elaborated by reaction with an alkyl halide in the presence of an inorganic base such as potassium carbonate in DMF, at elevated temperature. This provides compounds such as **S5-2**, as depicted in **Scheme 5**.

Scheme 6



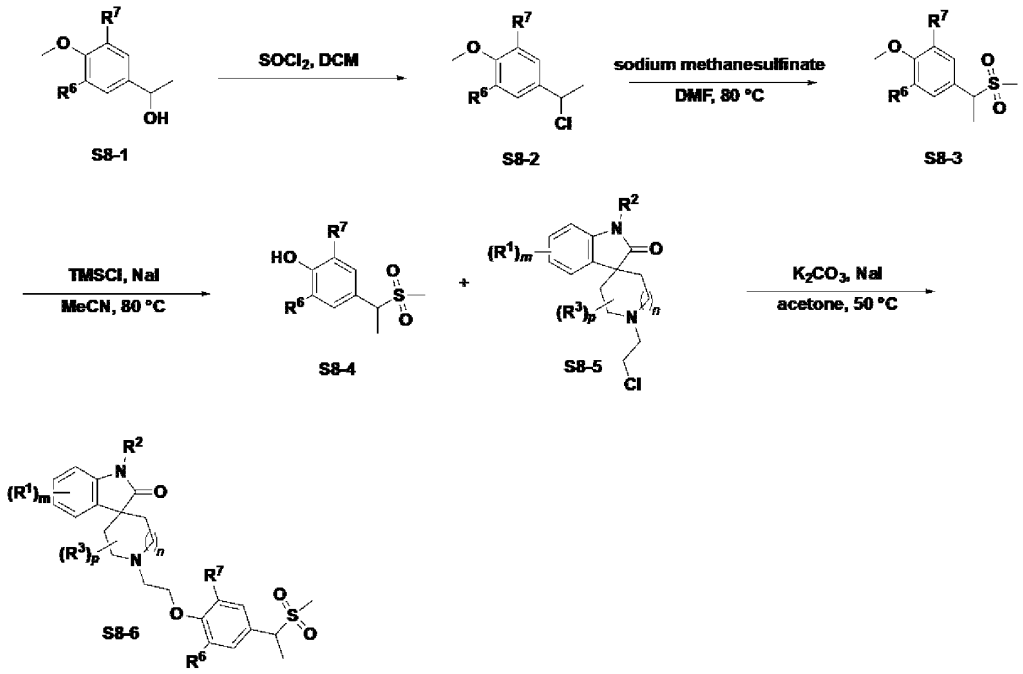
[0582] **Scheme 6** depicts an approach to compounds of formula **S6-5**. Alkylation of oxindole **S6-1** with an alkyl halide in the presence of a base such as potassium carbonate generates **S6-2**. Removal of the Boc group by treatment with a protic acid such as TFA in an aprotic solvent such as DCM generates amine **S6-3**, which can be further elaborated by coupling with an alkyl halide such as **S6-4**, according to procedures shown in **Scheme 1**.

Scheme 7



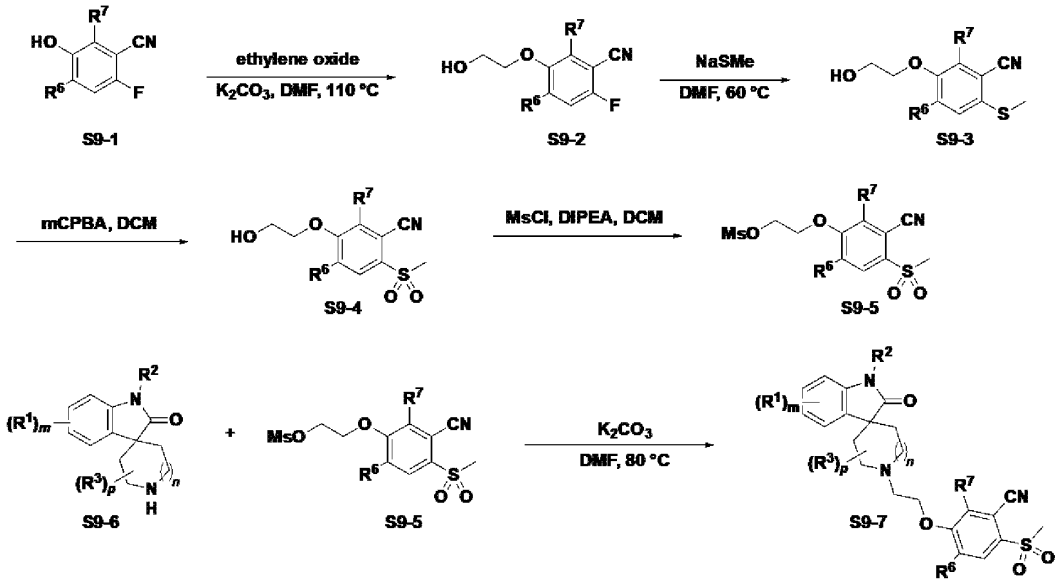
[0583] An alternative approach to compounds of formula **S7-3** involving reductive amination of ketone **S7-2** with amine **S7-2** under the action of sodium triacetoxyborohydride, titanium tetraisopropoxide and acetic acid, is depicted in **Scheme 7**.

Scheme 8



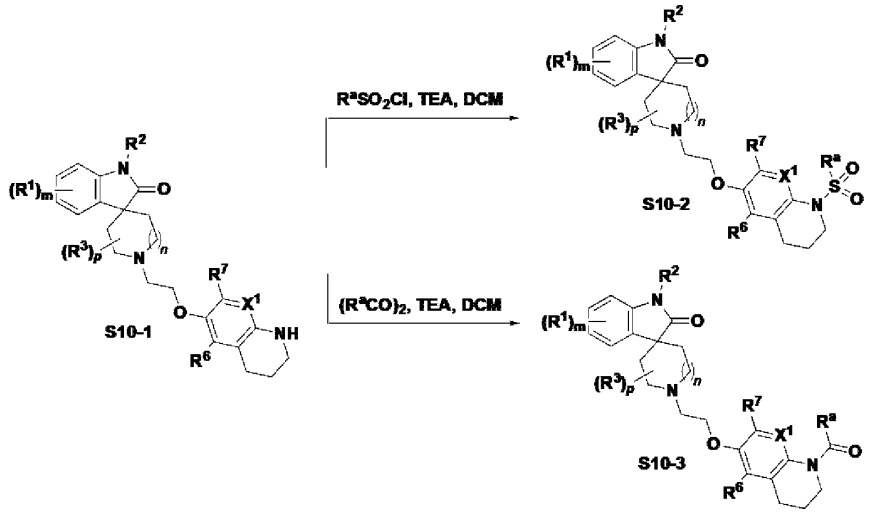
[0584] **Scheme 8** depicts an alternative approach to compounds of formula **S8-6**. Generation of benzylic chloride **S8-2** from benzylic alcohol **S8-1**, followed by introduction of a sulfonyl group, gives rise to compound **S8-3**. Deprotection of **S8-3** with in situ-formed TMSI gives phenol **S8-4**, which can be coupled with alkyl chloride **S8-5** in the presence of potassium carbonate and sodium iodide in acetone at elevated temperature. Single stereoisomers may be obtained by chiral SFC purification of **S8-6**.

Scheme 9



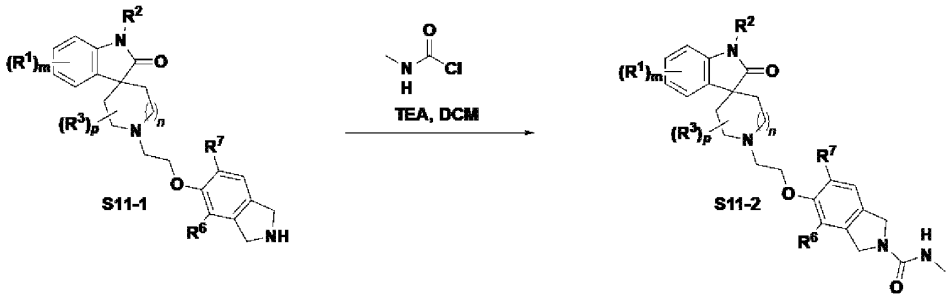
[0585] **Scheme 9** shows an approach to compounds of formula **S9-7**. Alkylation of phenol **S9-1** with ethylene oxide, followed by S_NAr reaction with sodium methanethiolate gives thioether **S9-3**. Oxidation with mCPBA gives sulfone **S9-4**. Treatment of **S9-4** with methanesulfonyl chloride and a tertiary amine base such as DIPEA gives **S9-5**, which can be converted to **S9-7** under conditions similar to **Scheme 1**.

Scheme 10



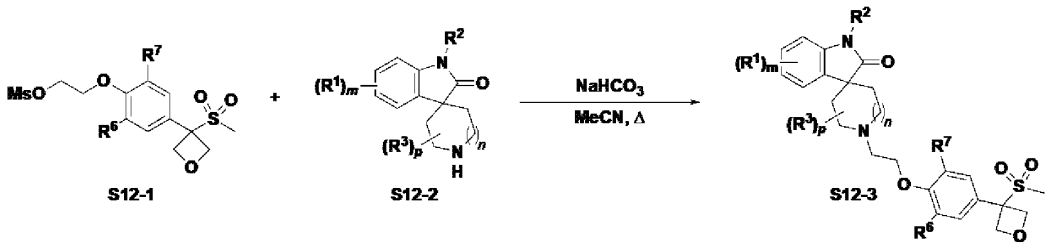
[0586] As shown in **Scheme 10**, compounds of formula **S10-1** may be further elaborated via coupling with a sulfonyl chloride such as methanesulfonyl chloride in the presence of triethylamine in DCM to provide **S10-2**. Compound **S10-1** may also be acylated with an anhydride such as acetic anhydride and triethylamine to generate **S10-3**.

Scheme 11



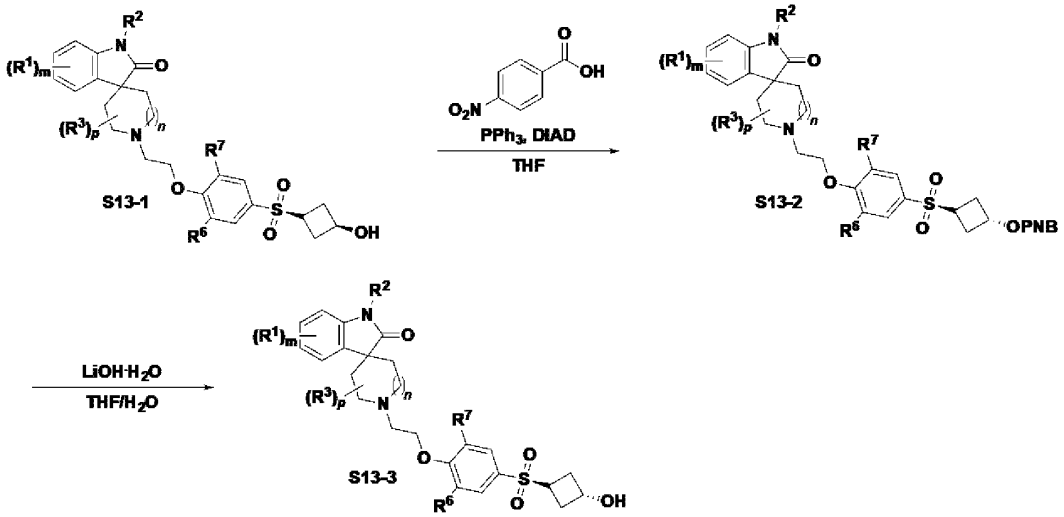
[0587] As shown in **Scheme 11**, compounds of formula **S11-1** may be elaborated via coupling with a carbamoyl chloride such as N-methylcarbamoyl chloride in the presence of triethylamine to give a urea of the formula **S11-2**.

Scheme 12



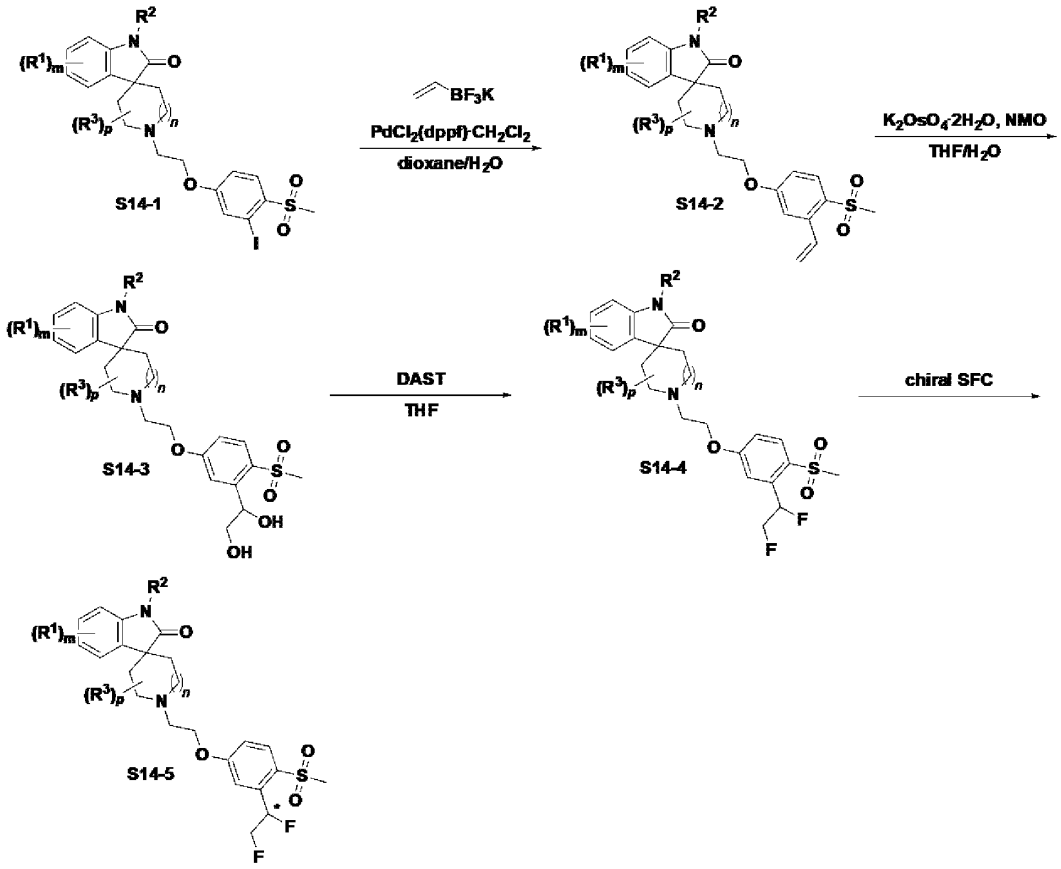
[0588] An alternative approach to compounds of formula **S12-3** is depicted in **Scheme 12**, via coupling of a mesylate such as **S12-1** and amine such as **S12-2** in acetonitrile using sodium bicarbonate as base.

Scheme 13



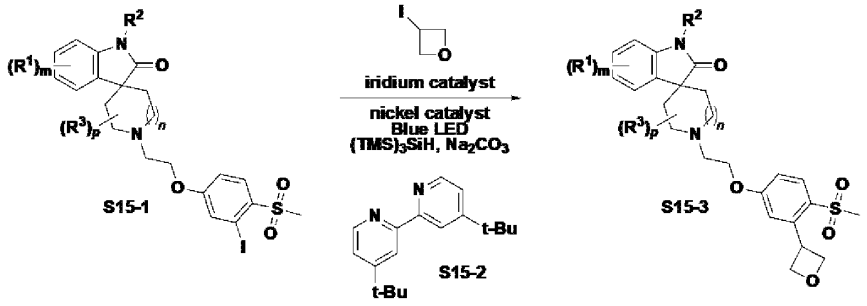
[0589] **Scheme 13** depicts the conversion of cis isomer **S13-1** to trans isomer **S13-3**. Mitsunobu coupling with p-nitrobenzoic acid generates ester **S13-2**, which can undergo hydrolysis with lithium hydroxide to generate the trans isomer **S13-3**.

Scheme 14



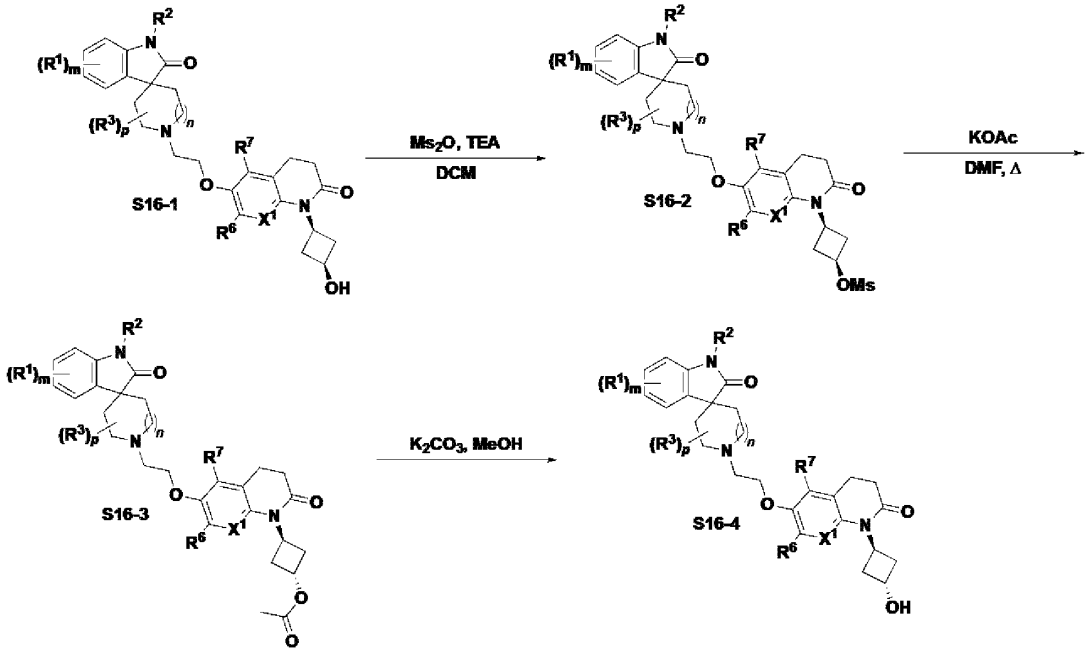
[0590] Elaboration of compounds of formula **S14-1** (generated using methods described in **Scheme 1**) is depicted in **Scheme 14**. Cross coupling of **S14-1** with potassium vinyltrifluoroborate using a palladium catalyst and an inorganic base provides olefin **S14-2**. Dihydroxylation with an osmium catalyst and NMO gives **S14-3**. Diol **S14-3** may be further modified by treatment with DAST, giving rise to difluoride **S14-4** as an isomeric mixture. Single isomer analogs such as **S14-5** may be obtained by chiral SFC purification.

Scheme 15



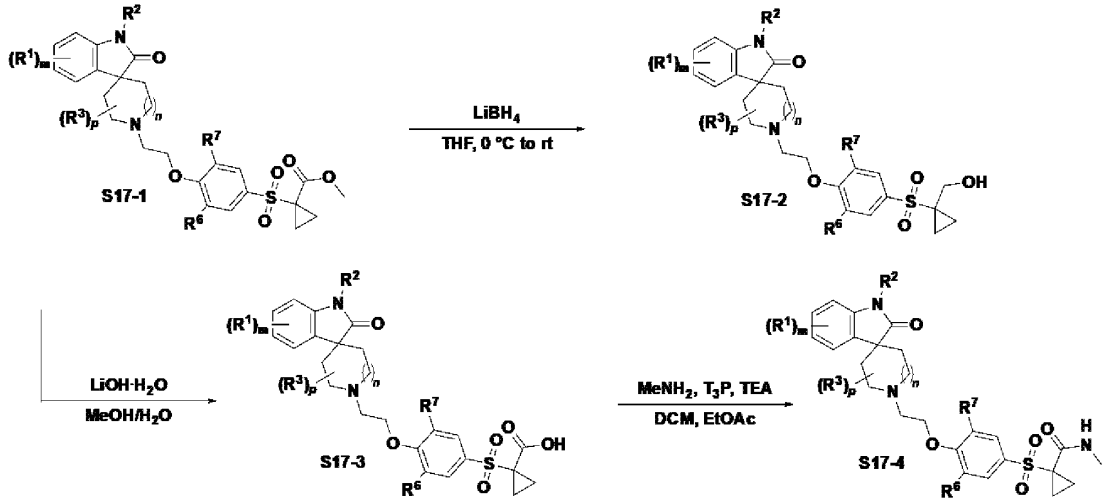
[0591] Iodide **S15-1** may be elaborated using photoredox methods outlined in **Scheme 15**. Coupling of **S15-1** and 3-iodooxetane can be achieved with nickel(II) chloride ethylene glycol dimethyl ether complex, ligand **S15-2**, (Ir[dF(CF_3)ppy]$_2$(dtbpy))PF_6, bis(trimethylsilyl)silyl-trimethylsilane, Na_2CO_3 and blue LED to generate **S15-3**.

Scheme 16



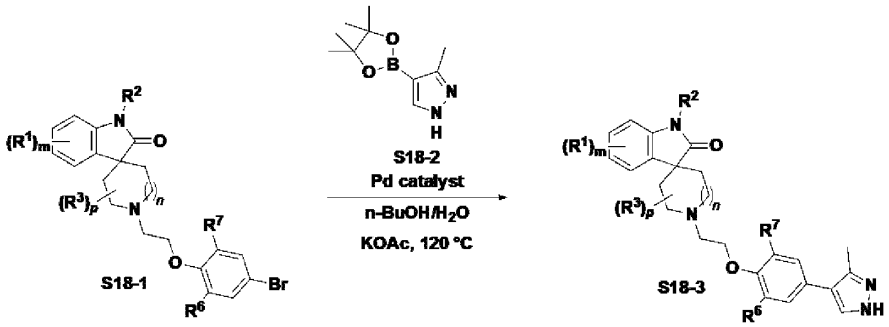
[0592] Conversion of cis-disubstituted cyclobutanol **S16-1** to the trans isomer **S16-4** is depicted in **Scheme 16**. Treatment with methanesulfonic anhydride and TEA generates mesylate **S16-2**. Heating with potassium acetate generates ester **S16-3**, which can be converted to the alcohol under the action of potassium carbonate in MeOH to give **S16-4**.

Scheme 17



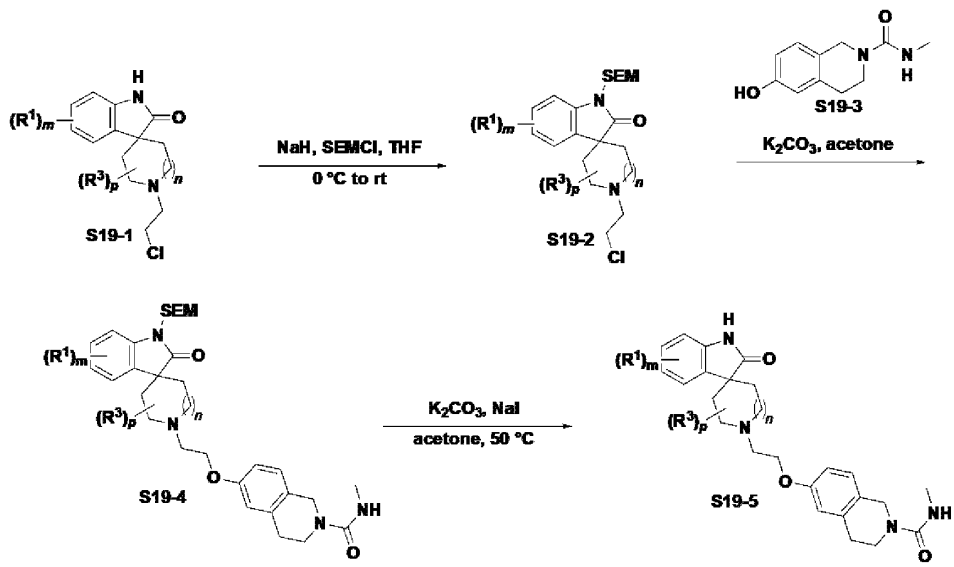
[0593] Compounds of the formula **S17-1** can be converted to the corresponding alcohol by treatment with a reducing agent such as $LiBH_4$, as depicted in **Scheme 17**. Alternatively, **S17-1** can underdo hydrolysis with lithium hydroxide to give acid **S17-3**. Amide bond formation with an amine such as methylamine under the action of T3P and TEA generates amide **S17-4**.

Scheme 18



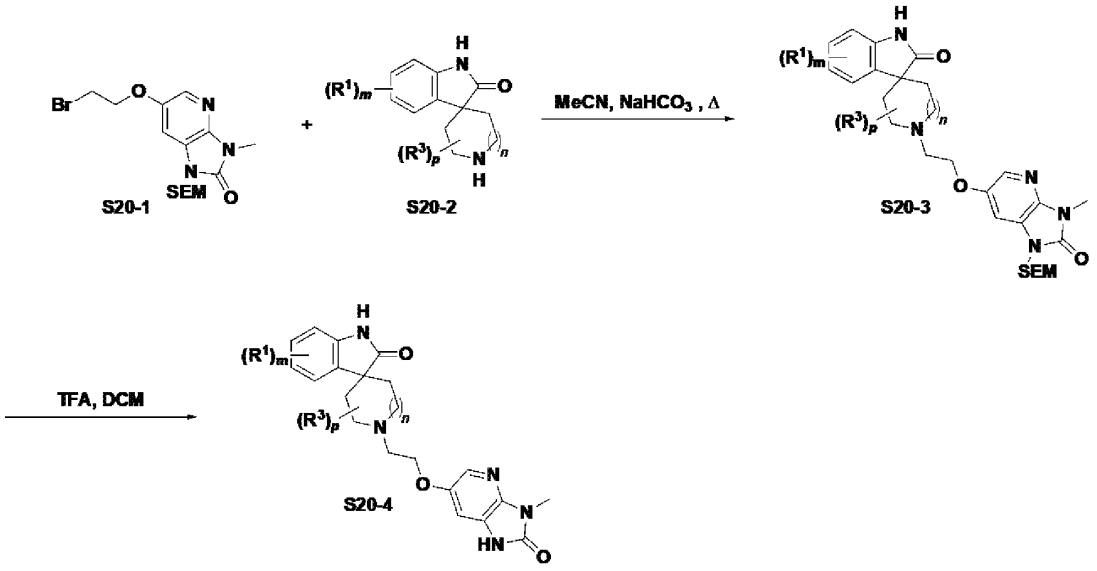
[0594] Compounds of formula **S18-1** can be elaborated by Suzuki couplings of boronate esters such as **S18-2**, a catalyst such as bis(4-(di-tert-butylphosphanyl)-N,N-dimethylaniline) dichloropalladium, and a base such as KOAc, as depicted in **Scheme 18**.

Scheme 19



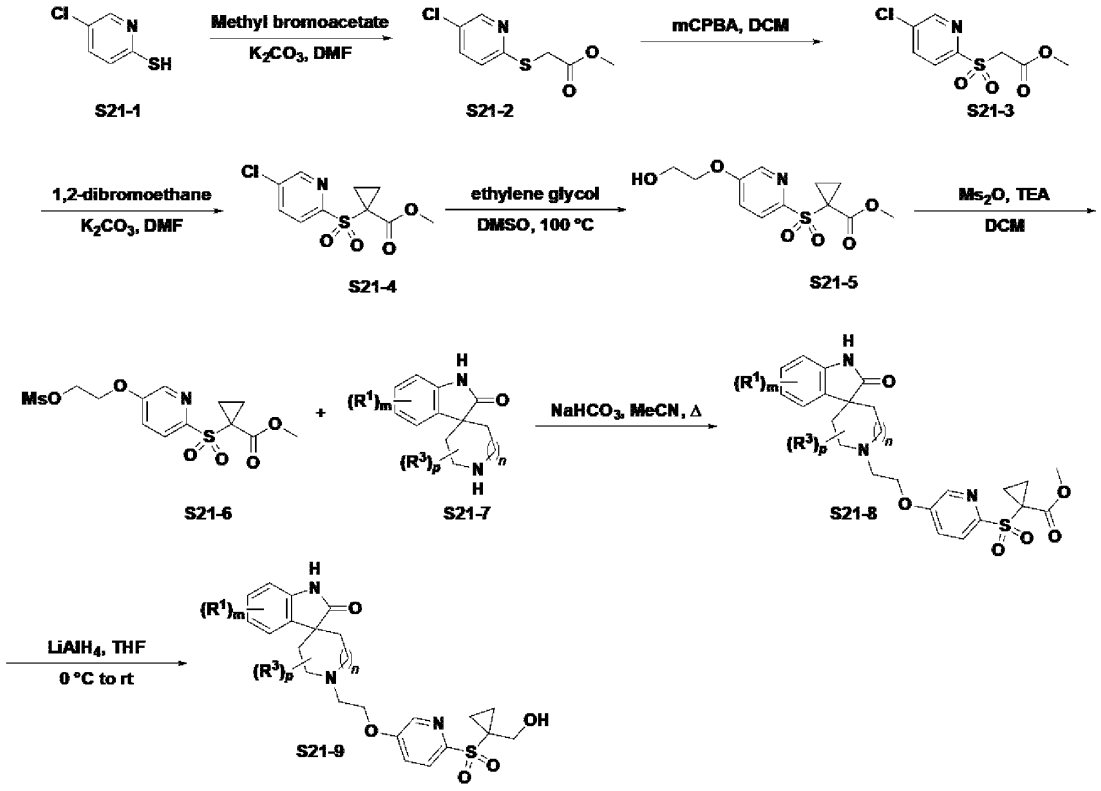
[0595] **Scheme 19** begins with protection of an oxindole nitrogen using sodium hydride and SEMCl to give **S19-2**. Coupling with a phenol such as **S19-3** gives **S19-4**. Removal of the SEM group is achieved by heating a mixture of **S19-4**, potassium carbonate, and NaI in acetone to give compound of formula **S19-5**.

Scheme 20



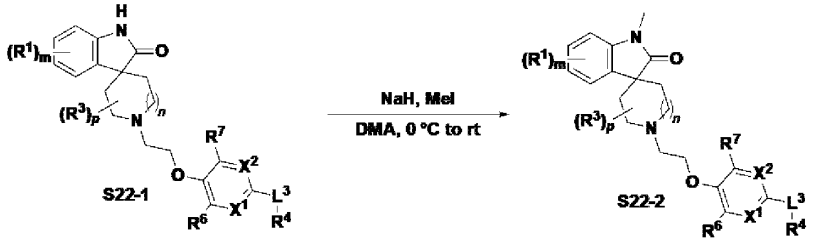
[0596] Heterocyclic electrophiles bearing protecting groups such as compound **S20-1** may be coupled with amine nucleophiles such as **S20-2** under the conditions shown in **Scheme 20**. Deprotection of a protecting group such as a SEM N-O acetal may be achieved by treatment of **S20-3** with a protic acid such as TFA to deliver **S20-4**.

Scheme 21



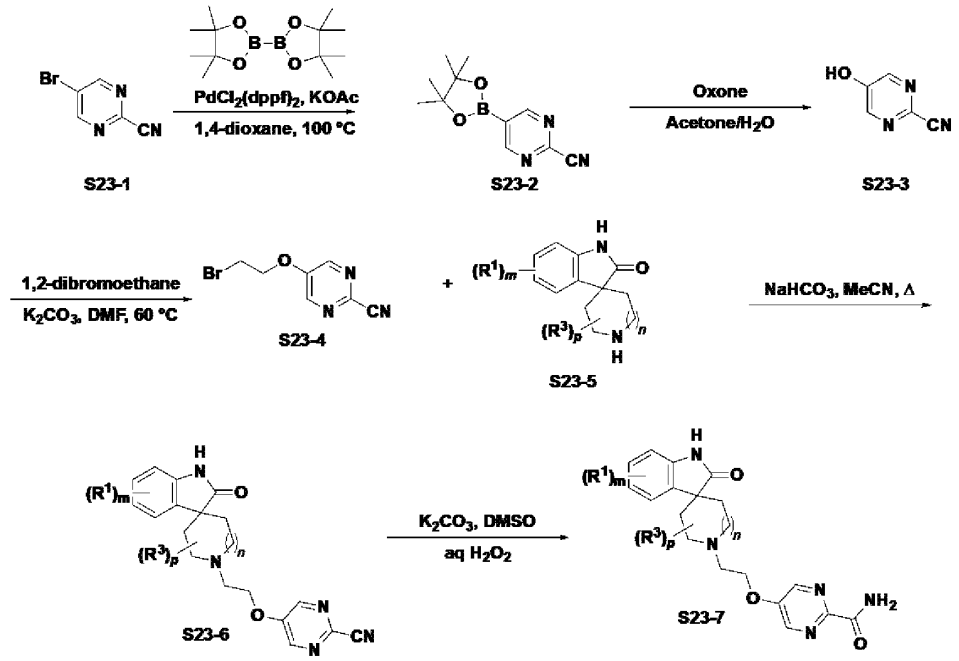
[0597] An approach to compounds of formula **S21-9** is shown in **Scheme 21**. Alkylation of thiol **S21-1** followed by oxidation to the sulfone generates compound **S21-3**. Cyclopropane formation via double alkylation in the presence of potassium carbonate gives **S21-4**. SNAr reaction with ethylene glycol and mesylation of **S21-5** provides compound **S21-6**, which can be coupled with amine **S21-7** under standard conditions (**Scheme 12**). Treatment of compound **S21-8** with a reducing agent such as $LiAlH_4$ gives compound **S21-9**.

Scheme 22



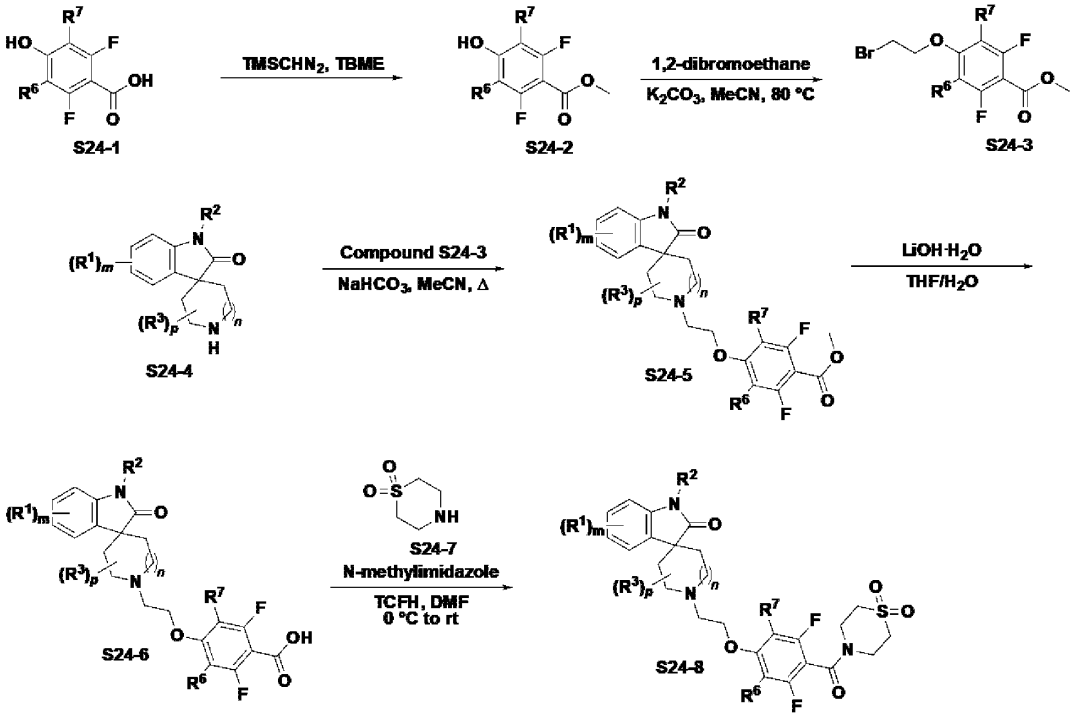
[0598] Compounds of formula **S22-2** may be obtained by treatment of compound **S22-1** with a base such as sodium hydride and an alkylating agent such as iodomethane, as depicted in **Scheme 22**.

Scheme 23.



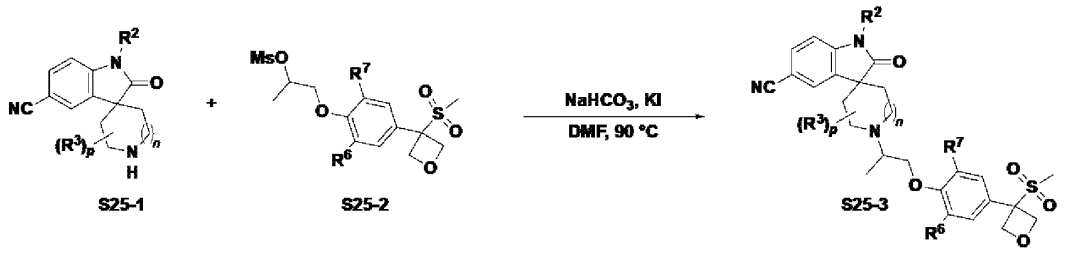
[0599] Primary amides of formula **S23-7** can be generated according to **Scheme 23**. Palladium-catalyzed borylation of pyrimidine **S23-1** followed by oxidation gives compound **S23-3**. Alkylation with 1,2-dibromoethane to provide **S23-4** and coupling with amine **S23-5** under conditions outlined above (**Scheme 12**) generates compound **S23-6**. Conversion of the nitrile to the primary amide **S23-7** occurs upon treatment with potassium carbonate and aqueous H_2O_2.

Scheme 24



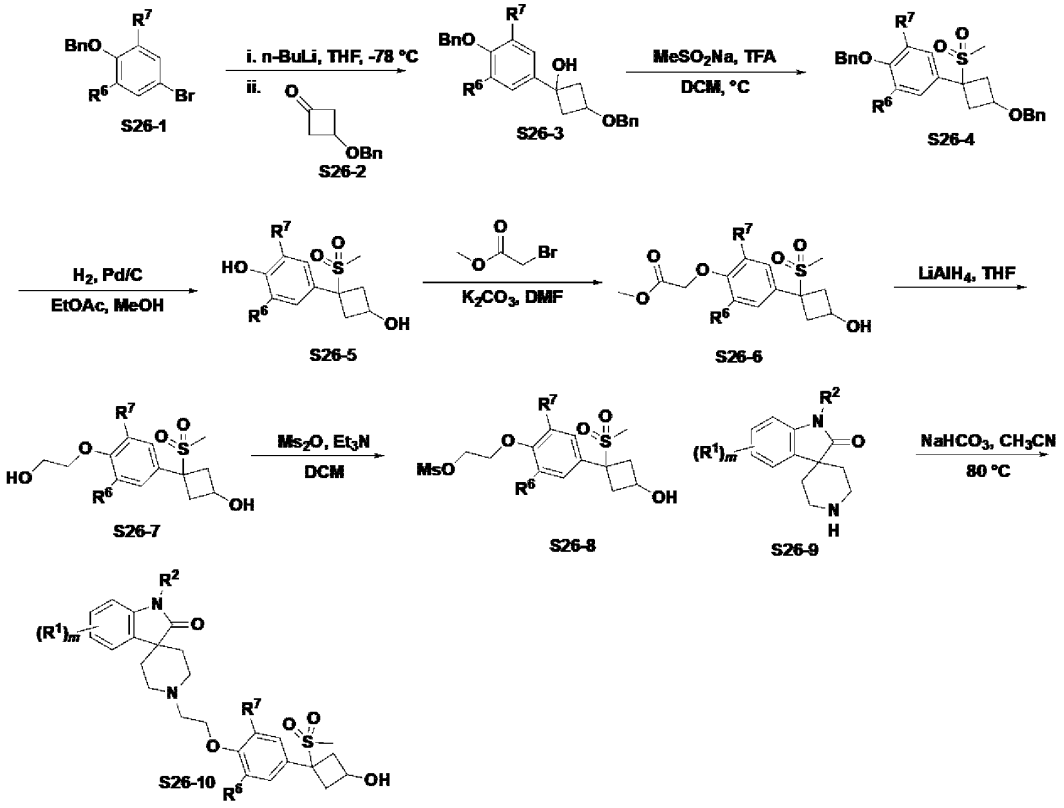
[0600] Compounds of formula **S24-8** can be synthesized according to **Scheme 24**. Esterification and alkylation of carboxylic acid **S24-1** provides alkyl bromide **S24-3**. Coupling with amine **S24-4** under standard conditions (**Scheme 12**) gives **S24-5**. Hydrolysis followed by amide bond formation with amine **S24-7**, using N-methyl imidazole and TCFH, gives **S24-8**.

Scheme 25



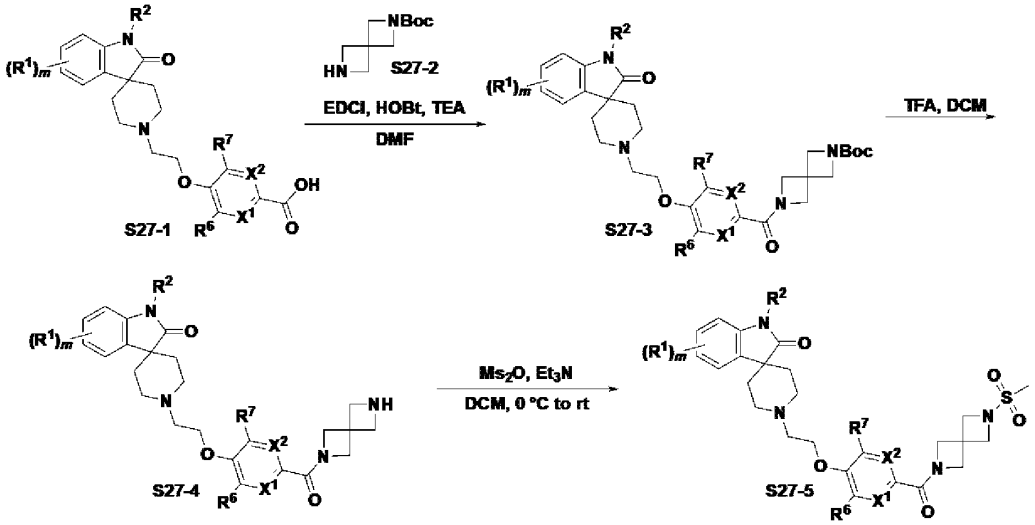
[0601] Compounds of formula **S25-3** may also be prepared by reaction of an amine such as **S25-1** with a secondary mesylate such as **S25-2** in the presence of $NaHCO_3$ and potassium iodide in DMF at elevated temperature, as depicted in **Scheme 25**. Compounds of formula **S25-3** may be further purified by chiral SFC to generate isomerically pure analogs.

Scheme 26



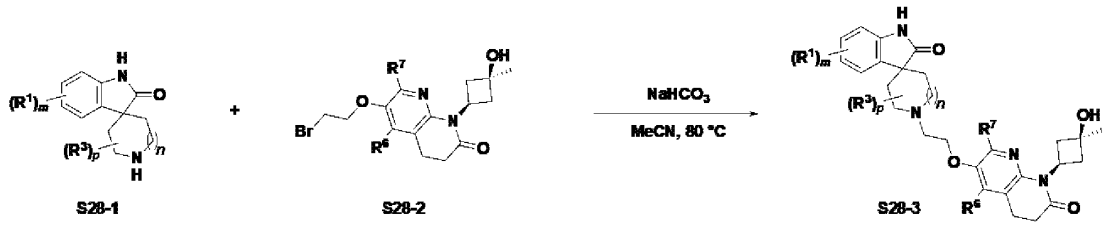
[0602] Compounds of formula **S26-10** may be prepared according to **Scheme 26**. Lithium-halogen exchange with aryl bromide **S26-1**, followed by addition to a ketone such as **S26-2**, gives alcohol **S26-3** as a mixture of cis and trans isomers. Reaction with sodium methanesulfinate and TFA gives sulfone **S26-4**. Removal of benzyl ethers by hydrogenation gives diol **S26-5**. Selective alkylation of the phenol moiety with bromoethyl acetate gives ester **S26-6**. Reduction with $LiAlH_4$ gives alcohol **S26-7**, which can be converted to **S26-8** and coupled with amine **S26-9** using procedures described above (**Scheme 12**). Further purification of **S26-10** to obtain single stereoiosmers may be achieved by methods such as reverse phase HPLC or chiral SFC.

Scheme 27



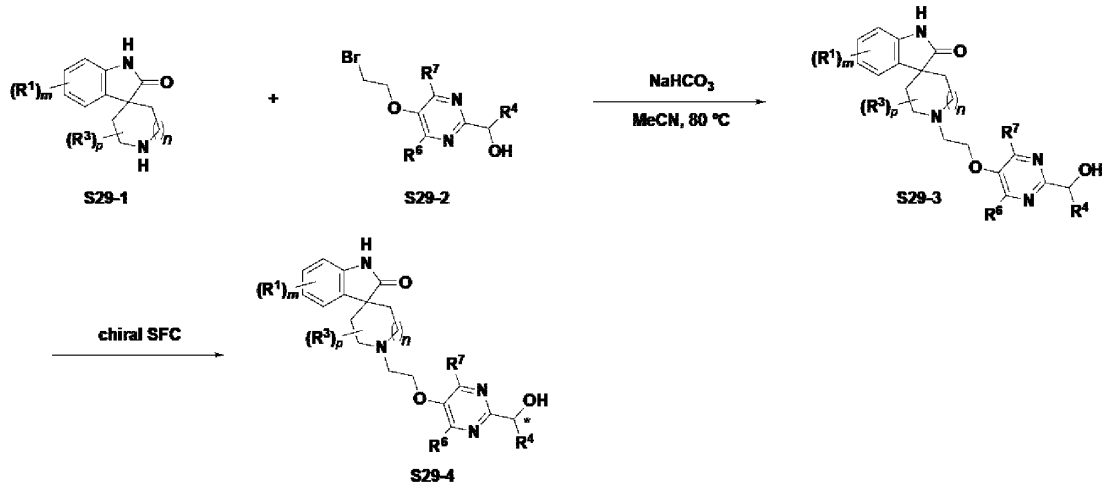
[0603] Compounds of formula **S27-5** can be prepared according to **Scheme 27**. Coupling of acid **S27-1** with an amine such as **S27-2** under the action of EDCI and HOBt gives amide **S27-3**. Treatment with a protic acid such as TFA gives amine **S27-4**. Amine **S27-4** may be further elaborated, such as by reaction with methanesulfonic anhydride and TEA, to give compounds such as **S27-5**.

Scheme 28



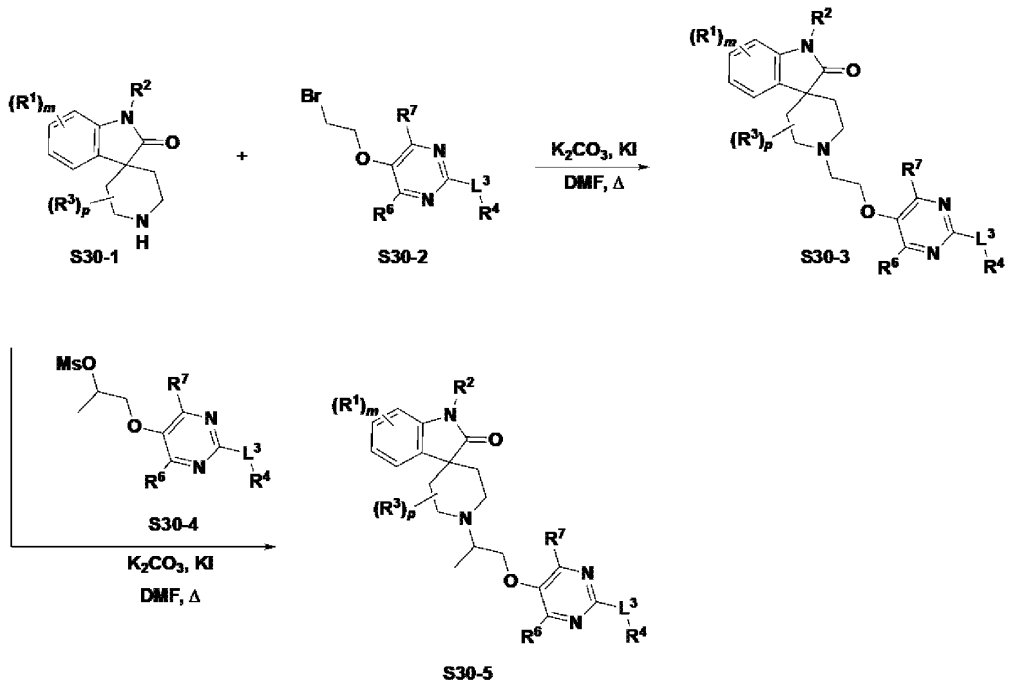
[0604] Compounds of formula **S28-3** can be prepared according to **Scheme 28**, using reaction conditions similar to those described above. Coupling of amine **S28-1** with azatetrahydronaphthyridinones bearing tertiary alcohol moieties such **S28-2** occurs upon heating in an aprotic solvent such as acetonitrile in the presence of an inorganic base such as sodium bicarbonate to give compounds of formula **S28-3**.

Scheme 29



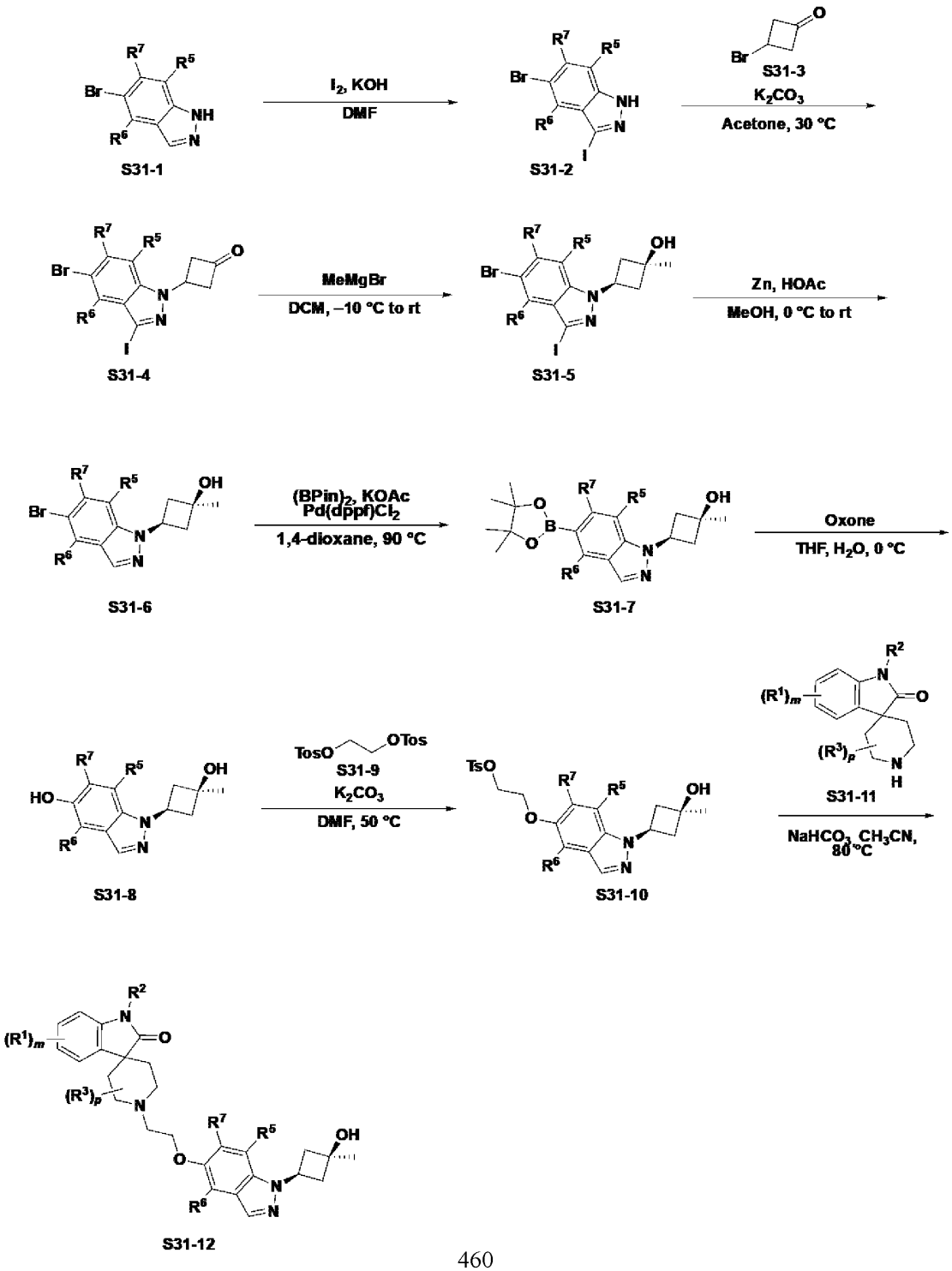
[0605] Compounds of formula **S29-4** may can be prepared according to **Scheme 29**. Reaction of amine **S29-1** with an alkyl bromide bearing a secondary alcohol such as **S29-2** occurs upon heating in an aprotic solvent such as acetonitrile in the presence of an inorganic base such as sodium bicarbonate to give compounds of formula **S29-3**. Further purification using methods such as chiral SFC may be used to generate single isomer analogs such as **S29-4**.

Scheme 30



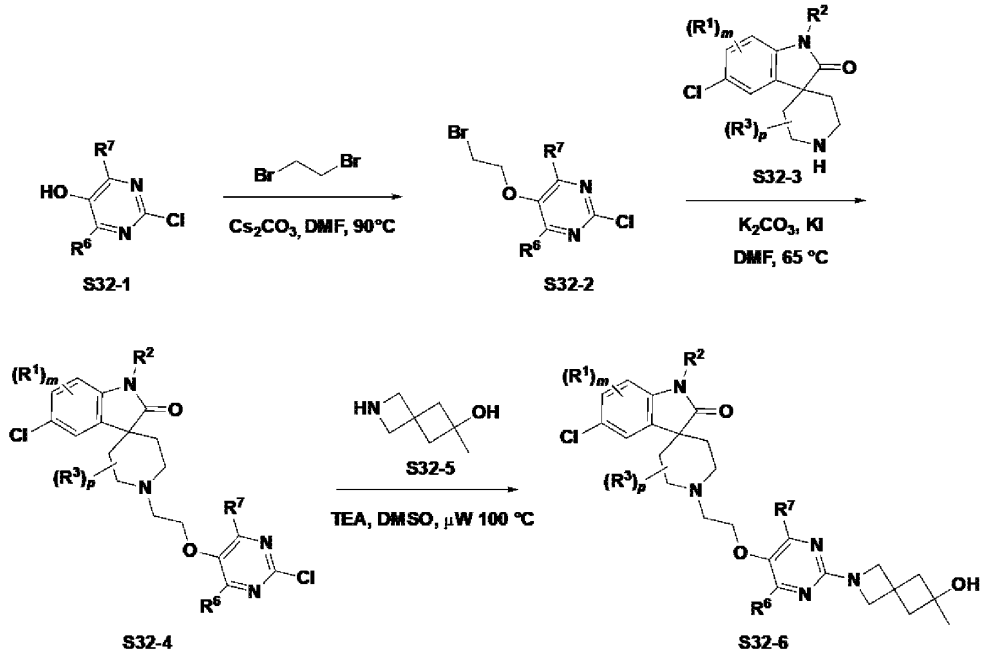
[0606] Compounds of formula **S30-3** and **S30-5**, which bear multiple substituents on the pyrimidine moiety, are depicted in **Scheme 30**. Thus, coupling of the amine HCl salt **S30-1** with alkyl halide **S30-2** may be achieved upon heating in an aprotic solvent such as DMF, in the presence of potassium carbonate and potassium iodide, to deliver compounds of formula **30-3**. Alternatively, coupling under identical reaction conditions as those described above with amine **S30-1** and a chiral center bearing intermediate such as **S30-4**, may give rise to compounds of the formula **S30-5**. If desired, further purification of **S30-5** may be achieved using methods such as chiral SFC.

Scheme 31


S31-1
I2, KOH
DMF
S31-2
S31-3
K2CO3
Acetone, 30 °C
S31-4
MeMgBr
DCM, –10 °C to rt
S31-5
Zn, HOAc
MeOH, 0 °C to rt
S31-6
(BPin)2, KOAc
Pd(dppf)Cl2
1,4-dioxane, 90 °C
S31-7
Oxone
THF, H2O, 0 °C
S31-8
S31-9
K2CO3
DMF, 50 °C
S31-10
S31-11
NaHCO3, CH3CN,
80 °C
S31-12

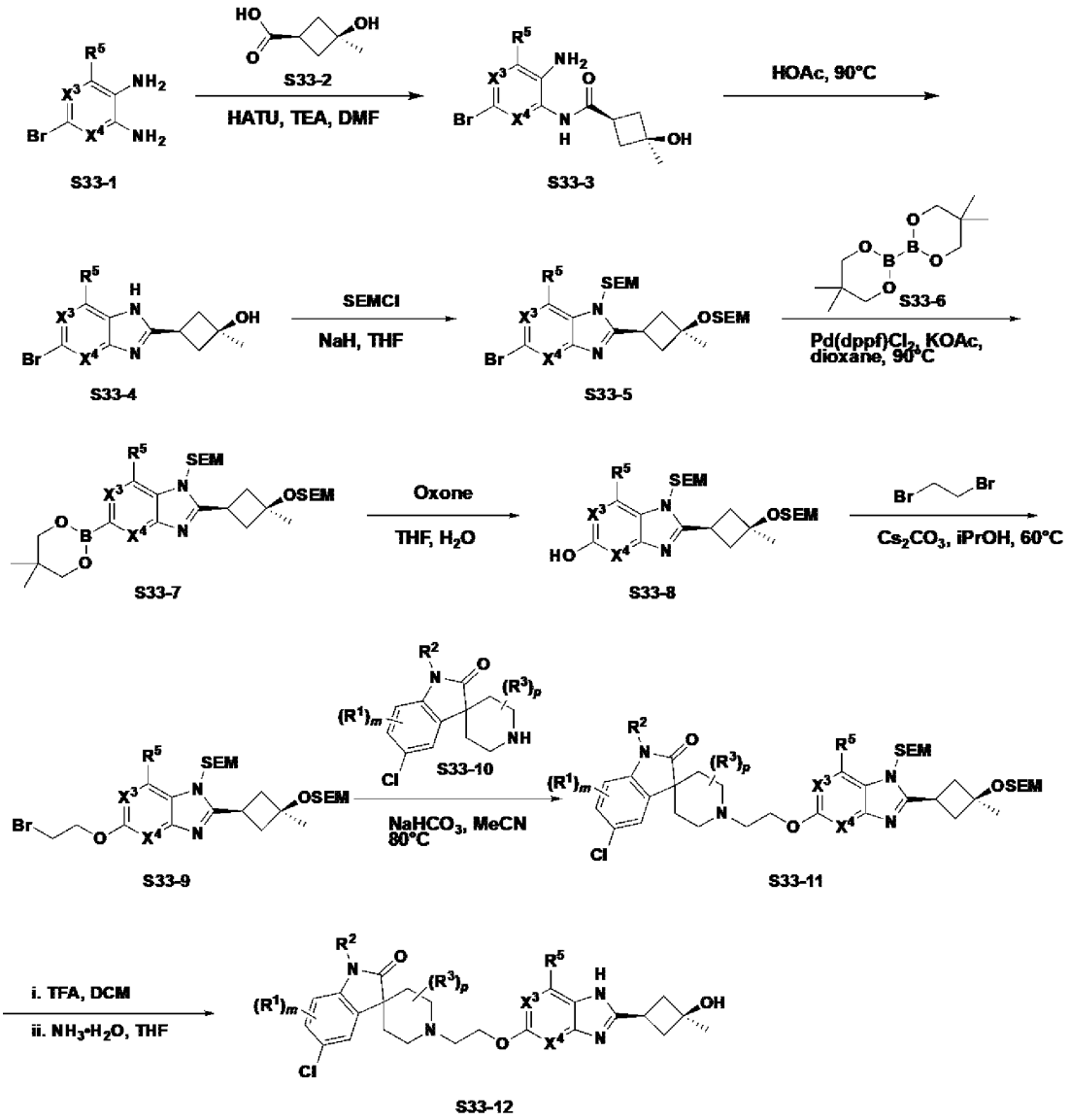
[0607] Compounds of formula **S31-12** may be prepared according to **Scheme 31**. Treatment of indazole **S31-1** with iodine and potassium hydroxide in a solvent such as DMF provides **S31-2**. Alkylation of **S31-2** with an electrophile such as **S31-3** occurs in the presence of an inorganic base such as potassium carbonate in warm acetone to give **S31-4**. Treatment with a Grignard reagent such as methylmagnesium bromide at –10 °C in a solvent such as DCM gives tertiary alcohol **S31-5**. Protodeiodination occurs on treatment with Zn metal and acetic acid in methanol to give **S31-6**. Palladium catalyzed borylation may be conducted in a solvent such as 1,4-dioxane by reaction with Bis(pinacolato)diboron, potassium acetate as base, and a palladium catalyst such as [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) to give **S31-7**. Reaction with Oxone gives rise to alcohol **S31-8**. Phenol alkylation occurs on treatment with an electrophile such as bis-tosylate **S31-9** to give **S31-10**. Heating a mixture of **S31-10**, an amine nucleophile such as **S31-11**, and an inorganic base such as sodium bicarbonate in a solvent such as acetonitrile gives compounds of formula **S31-12**.

Scheme 32



[0608] Compounds of formula **S32-6** may be prepared according to **Scheme 32**. Heating a mixture of **S32-1**, 1,2-dibromoethane, and an inorganic base such as cesium carbonate gives **S32-2**. Heating a mixture of **S32-2**, an amine nucleophile such as **S32-3**, an inorganic base such as potassium bicarbonate, and potassium iodide in a solvent such as DMF gives compounds of formula **S32-4**. Compounds of formula **S32-4** may be further elaborated by S_NAr reaction with an amine such as **S32-5**, a tertiary amine base such as triethylamine, in DMSO at 100 °C in a microwave reactor to give compounds of formula **S32-6**.

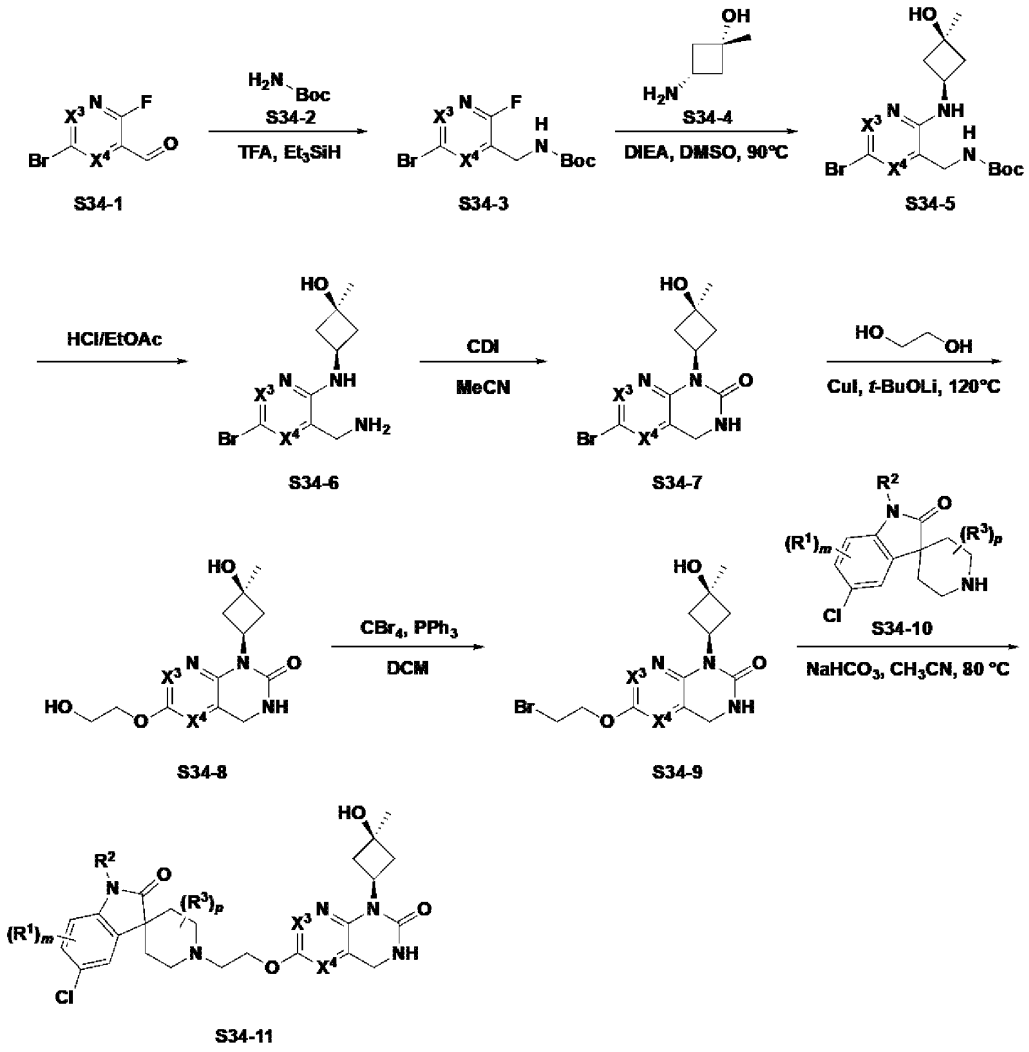
Scheme 33



[0609] Compounds of formula **S33-12** may be prepared according to **Scheme 33**. Reaction of diamine derivative **S33-1** with a carboxylic acid such as **S33-2** gives amide **S33-3**. Cyclization to benzimidazole **S33-4** may be achieved by heating **S33-3** in acetic acid. Treatment of **S33-4** with an excess of 2-(Trimethylsilyl)ethoxymethyl chloride and sodium hydride in an aprotic solvent such as THF gives **S33-5**. Palladium catalyzed borylation may be conducted in a solvent such as 1,4-dioxane by reaction with diboron reagent **S33-6**, potassium acetate as base, and a palladium catalyst

such as [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) to give **S33-7**. Treatment with Oxone in a mixed solvent such as THF and water gives **S33-8**. Alkylation with 1,2-dibromoethane in the presence of an inorganic base such as cesium carbonate gives **S33-9**. **S33-9** may be coupled with amine **S33-10** in hot acetonitrile in the presence of a base such as sodium bicarbonate to give **S33-11**. SEM-protecting group removal is achieved by treatment with a protic acid such as TFA, to give a benzimidazole which may then be converted to the free base by treatment with aqueous ammonia to deliver compounds of formula **S33-12**.

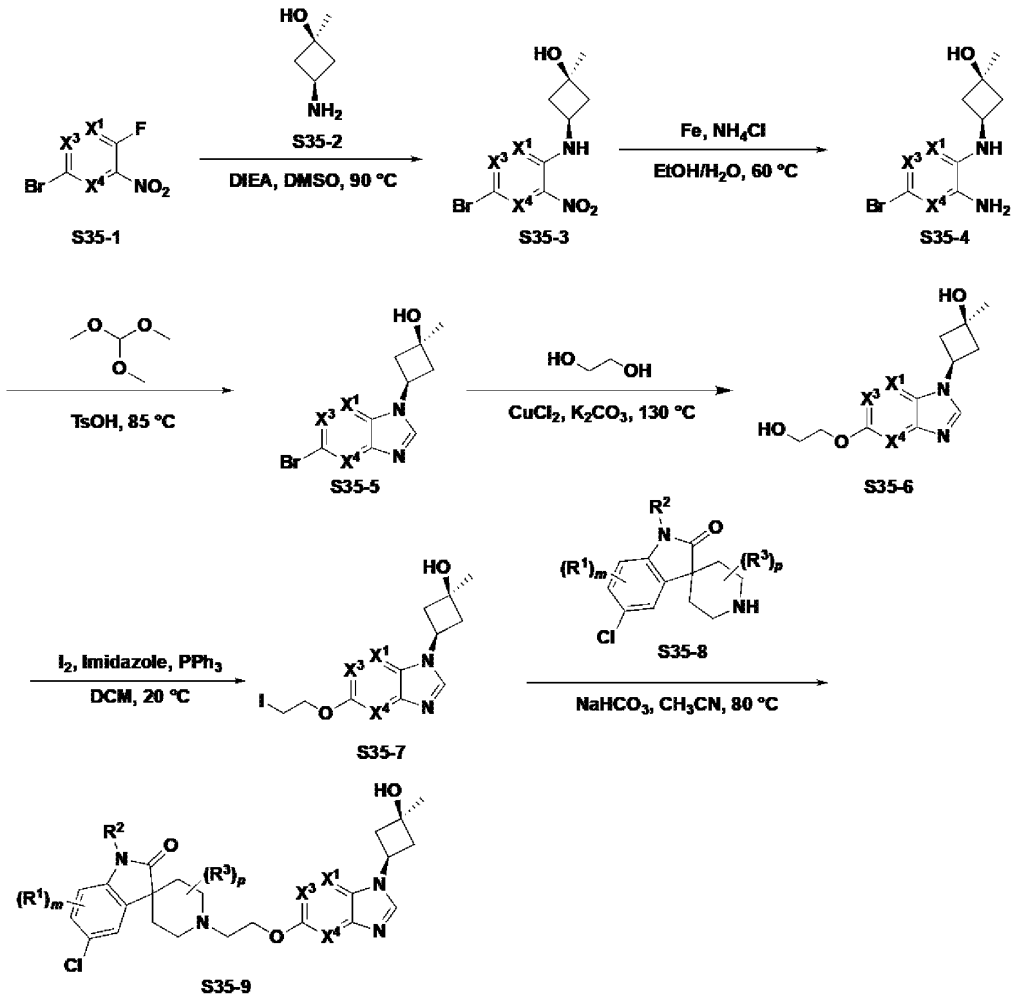
Scheme 34



[0610] Compounds of formula **S34-11** may be prepared according to **Scheme 34**. Reductive amination of an ortho-fluoro aldehyde such as **S34-1** with an amine such as **S34-2** with TFA and triethylsilane gives **S34-3**. SNAr reaction with an amine such as **S34-4** occurs upon heating with DIEA in DMSO to give **S34-5**. Removal of the Boc-protecting group by treatment with a protic acid such as HCl in an aprotic solvent such as EtOAc gives amine **S34-6**, which can undergo conversion to the cyclic urea on treatment with CDI to give **S34-7**. Heating **S34-7** in ethylene glycol, copper(I) iodide, and lithium tert-butoxide gives alcohol **S34-8**. Conversion of the alcohol moiety to an alkyl bromide may be achieved by reaction with carbon tetrabromide and triphenyl

phosphine in a solvent such as DCM to give **S34-9**. **S34-9** may be coupled with amine **S34-10** in hot acetonitrile in the presence of a base such as sodium bicarbonate to give compounds of formula **S34-11**.

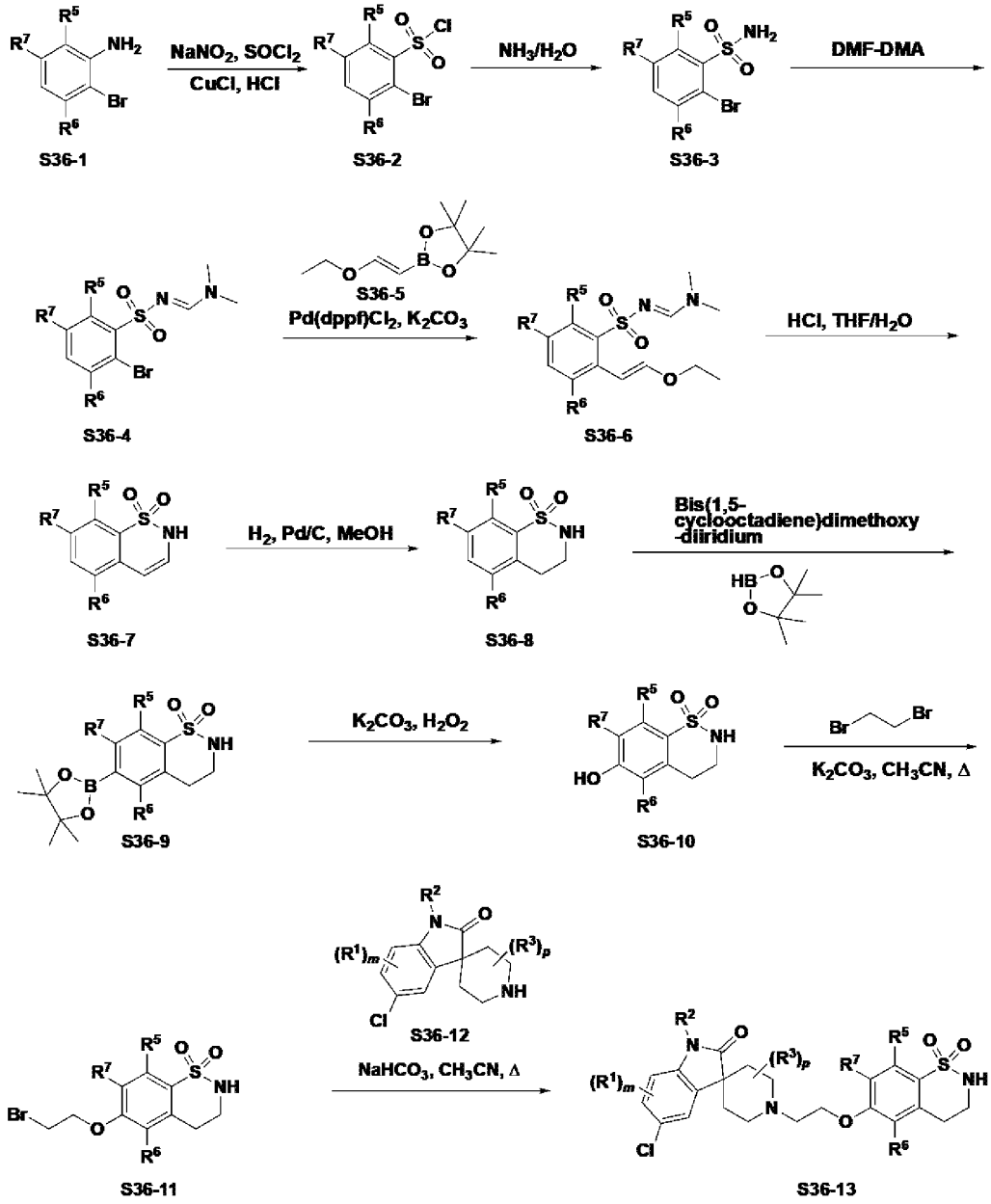
Scheme 35



[0611] Compounds of formula **S35-9** may be prepared according to **Scheme 35**. SNAr reaction between **S35-1** and amine **S35-2** occurs upon heating with a tertiary amine base such as DIEA in DMSO solvent to give **S35-3**. Nitro group reduction by heating with iron and ammonium chloride in a mixed solvent such as ethanol and water gives **S35-4**. **S35-4** is then converted to benzimidazole

derivative **S35-5** by heating in trimethyl orthoformate in the presence of p-toluene sulfonic acid. Heating **S35-5** in ethylene glycol in the presence of copper (II) chloride and potassium carbonate gives the primary alcohol **S35-6**. Conversion to the alkyl iodide by treatment with iodine, imidazole, and triphenyl phosphine provides **S35-7**. **S35-7** may be coupled with amine **S35-8** in hot acetonitrile in the presence of a base such as sodium bicarbonate to give compounds of formula **S35-9**.

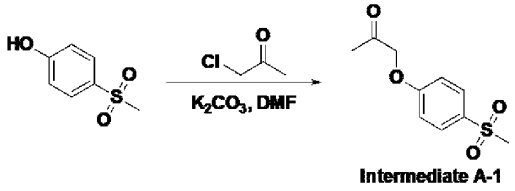
Scheme 36



[0612] Compounds of formula **S36-13** may be prepared according to **Scheme 36**. Conversion of anilne **S36-1** to corresponding sulfonyl chloride **S36-2** occurs upon treatment with sodium nitrite, thionyl chloride, copper(I) chloride, and HCl. Reaction of **S36-2** with aqueous ammonia provides sulfonamide **S36-3**. Reaction with N,N-dimethylformamide dimethyl acetal then generates N-

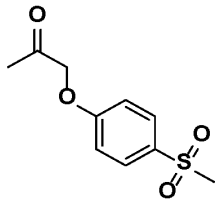
sulfonylformamidine **S36-4**. Suzuki coupling with a vinyl boronate ester such as **S36-5** gives enol ether **S36-6**. Treatment with HCl leads to hydrolysis of the formamidine and enol ether and cyclization to give **S36-7**. Hydrogenation of **S36-7** with Pd/C as catalyst gives **S36-8**. C-H oxidation of **S36-8** with pinacol borane in the presence of catalyst Bis(1,5-cyclooctadiene)dimethoxydiiridium gives **S36-9**, which may undergo oxidation upon treatment with H_2O_2 and potassium carbonate to give phenol derivative **S36-10**. **S36-10** undergoes alkylation with 1,2-dibromoethane under conditions described above to deliver **S36-11**. Coupling of **S36-11** with amine **S36-12** under conditions described above gives compounds of formula **S36-13**.

General Procedure for Intermediate A-1



Intermediate A-1

Step 1: 1-(4-methanesulfonylphenoxy)propan-2-one

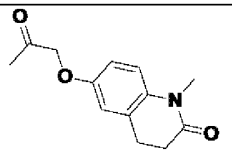


[0613] A mixture of 4-methylsulfonylphenol (500 mg, 2.90 mmol), 1-chloropropan-2-one (268 mg, 2.90 mmol) and K_2CO_3 (521 mg, 3.77 mmol) in DMF (10 mL) was stirred for 3 h. The reaction mixture was cooled to 0 °C and H_2O (20 mL) was added. The biphasic mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with H_2O (20 mL), brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give 1-(4-methylsulfonylphenoxy)propan-2-one (**Intermediate A-1**), which was taken to the next step without further purification. MS = 229.1 $[M+H]^+$.

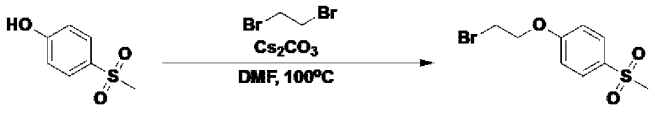
[0614] The following intermediate in Table 2 was prepared according to procedures similar those described for **Intermediate A-1** using the appropriate starting materials.

General Procedure for Intermediate A-2

Table 2.

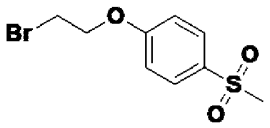
Intermediate #	Structure	IUPAC Name	Exact Mass $[M+H]^+$
A-2		1-methyl-6-(2-oxopropoxy)-1,2,3,4-tetrahydroquinolin-2-one	Calc'd 234.1 Found 234.2

General Procedure for Intermediate A-3



Intermediate A-3

Step 1: 1-(2-bromoethoxy)-4-methanesulfonylbenzene:

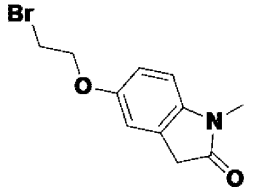
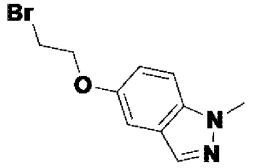
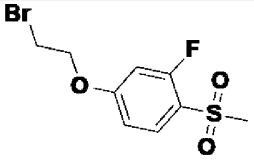
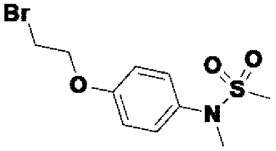
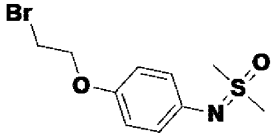
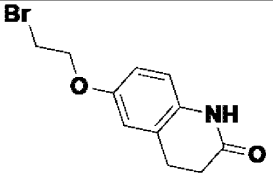


[0615] To a solution of 4-(methylsulfonyl)phenol (5.00 g, 29.0 mmol) in DMF (50 mL) were added Cs_2CO_3 (18.9 g, 58.1 mmol) and 1,2-dibromoethane (11.0 mL, 145 mmol). The mixture was stirred at 100 °C for 4 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (250 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 40 g cartridge, 0–60% EtOAc:petroleum ether). The crude product was triturated with MTBE (10 mL) to give 1-(2-bromoethoxy)-4-methanesulfonylbenzene (**Intermediate A-3**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.85 (d, J = 7.2 Hz, 2H), 7.19 (d, J = 6.8 Hz, 2H), 4.44 (t, J = 4.2 Hz, 2H), 3.84 (t, J = 4.2 Hz, 2H), 3.16 (s, 3H). MS = 279.0 / 281.0 $[M+H]^+$.

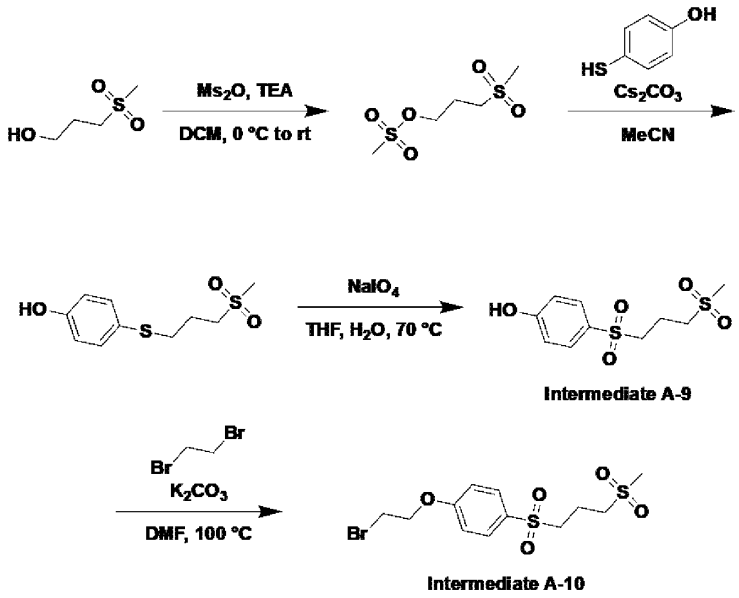
[0616] The following intermediates in Table 3 were prepared according to procedures similar to steps described for **Intermediate A-3** using the appropriate starting materials.

General Procedure for Intermediates A-4 to A-8 & A-83

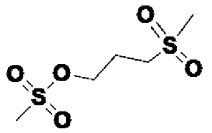
Table 3.

Intermediate #	Structure	IUPAC Name	Exact Mass $[M+H]^+$
A-4		5-(2-bromoethoxy)-1-methyl-2,3-dihydro-1H-indol-2-one	Calc'd 270.0 Found 270.0
A-5		5-(2-bromoethoxy)-1-methyl-1H-indazole	Calc'd 255.0 Found 255.0
A-6		4-(2-bromoethoxy)-2-fluoro-1-methanesulfonylbenzene	No charge in LCMS
A-7		*N*-[4-(2-bromoethoxy)phenyl]-*N*-methylmethanesulfonamide	Calc'd 308.0 Found 308.0
A-8		{[4-(2-bromoethoxy)phenyl]imino}dimethyl-λ^6-sulfanone	Calc'd 292.0 Found 292.0
A-83		6-(2-bromoethoxy)-1,2,3,4-tetrahydroquinolin-2-one	Calc'd 270.0 / 272.0 Found 270.0 / 271.9

General Procedure for Intermediates A-9 and A-10

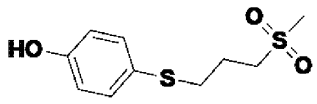


Step 1: 3-methanesulfonylpropyl methanesulfonate



[0617] To a 0 °C solution of 3-methanesulfonylpropan-1-ol (500 mg, 3.62 mmol) in DCM (5 mL) were added TEA (1.01 mL, 7.24 mmol) and methanesulfonic anhydride (945 mg, 5.43 mmol). The mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was quenched with H_2O (20 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give 3-methanesulfonylpropyl methanesulfonate, which was used in the next step without further purification.

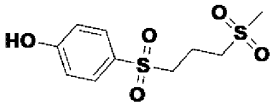
Step 2: 4-[(3-methanesulfonylpropyl)sulfanyl]phenol



[0618] To a mixture of 4-sulfanylphenol (319 mg, 2.52 mmol) and 3-methanesulfonylpropyl methanesulfonate (390 mg, 1.80 mmol) in MeCN (10 mL) was added Cs_2CO_3 (705 mg, 2.16 mmol). The mixture was stirred for 2 h, then was diluted with H_2O (10 mL) and extracted with EtOAc (3 x

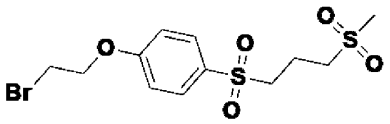
10 mL). The combined organic layers were washed with brine (12 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 4 g cartridge, 0–60% EtOAc:petroleum ether) to give 4-[(3-methanesulfonylpropyl)sulfanyl]phenol. MS = 245.1 $[M–H]^-$.

Step 3: 4-(3-methanesulfonylpropanesulfonyl)phenol



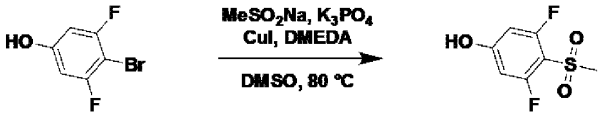
[0619] To a solution of 4-[(3-methanesulfonylpropyl)sulfanyl]phenol (370 mg, 1.50 mmol) in THF (3 mL) and H_2O (3 mL) was added $NaIO_4$ (250 µL, 4.51 mmol). The mixture was stirred at 70 °C for 12 h. After cooling to room temperature, the reaction mixture was quenched with saturated aqueous Na_2SO_3 (20 mL), then extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 4 g cartridge, 0–60% EtOAc:petroleum ether) to give 4-(3-methanesulfonylpropanesulfonyl)phenol (**Intermediate A-9**). MS = 277.1 $[M–H]^-$.

Step 4: 1-(2-bromoethoxy)-4-(3-methanesulfonylpropanesulfonyl)benzene



[0620] To a solution of 4-(3-methanesulfonylpropanesulfonyl)phenol (**Intermediate A-9**) (300 mg, 1.08 mmol) in DMF (3 mL) were added K_2CO_3 (223 mg, 1.62 mmol) and 1,2-dibromoethane (407 µL, 5.39 mmol). The mixture was stirred at 100 °C for 12 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (8 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by preparative TLC (SiO_2, 1:1 EtOAc:petroleum ether) to give 1-(2-bromoethoxy)-4-(3-methanesulfonylpropanesulfonyl)benzene (**Intermediate A-10**). ^1H NMR (400 MHz, DMSO-d_6): δ 7.84 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.8 Hz, 2H), 4.47 (t, J = 4.8 Hz, 2H), 3.86 (t, J = 5.2 Hz, 2H), 3.43 (t, J = 5.2 Hz, 2H), 3.22 (t, J = 7.6 Hz, 2H), 2.98 (s, 3H), 2.00–1.92 (m, 2H).

General Procedure for Intermediate A-11



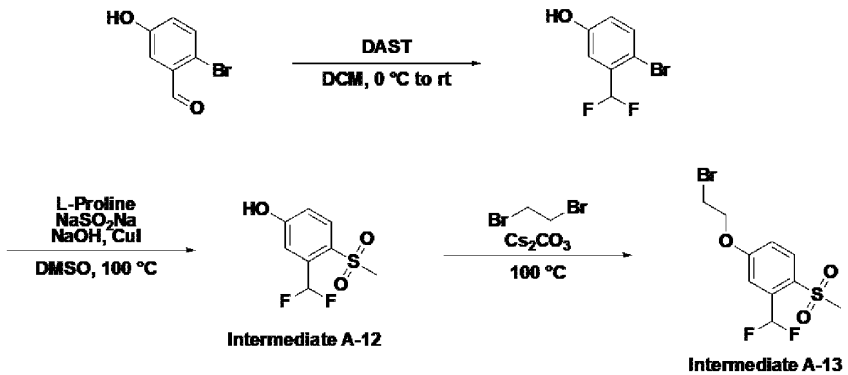
Intermediate A-11

Step 1: 3,5-difluoro-4-methanesulfonylphenol



[0621] To a solution of 4-bromo-3,5-difluorophenol (1.00 g, 4.78 mmol) and $MeSO_2Na$ (4.88 g, 47.8 mmol) in DMSO (15 mL) were added CuI (91.1 mg, 0.478 mmol), DMEDA (84 mg, 0.956 mmol) and K_3PO_4 (203 mg, 0.956 mmol). The mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–50% EtOAc:petroleum ether) to give the crude product. The product was further purified by reverse phase preparative HPLC (Agela C_{18} column, 5–35% Methanol: 0.04% HCl in H_2O) to give 3,5-difluoro-4-methanesulfonylphenol **(Intermediate A-11)**. MS = 207.1 $[M–H]^-$.

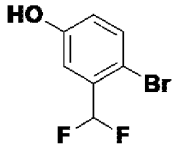
General Procedure for Intermediates A-12 and A-13



Intermediate A-12

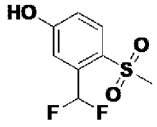
Intermediate A-13

Step 1: 4-bromo-3-(difluoromethyl)phenol



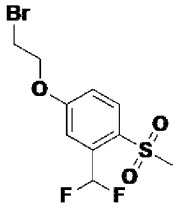
[0622] To a 0 °C solution of 2-bromo-5-hydroxybenzaldehyde (17.6 g, 87.5 mmol) in DCM (170 mL) was added DAST (14.1 g, 87.6 mmol) in one portion. The mixture was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was cooled to 0 °C, quenched with saturated aqueous $NaHCO_3$ (150 mL), and extracted with DCM (2 x 100 mL). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 120 g cartridge, 8–15% EtOAc:petroleum ether) to give 4-bromo-3-(difluoromethyl)phenol.

Step 2: 3-(difluoromethyl)-4-methanesulfonylphenol



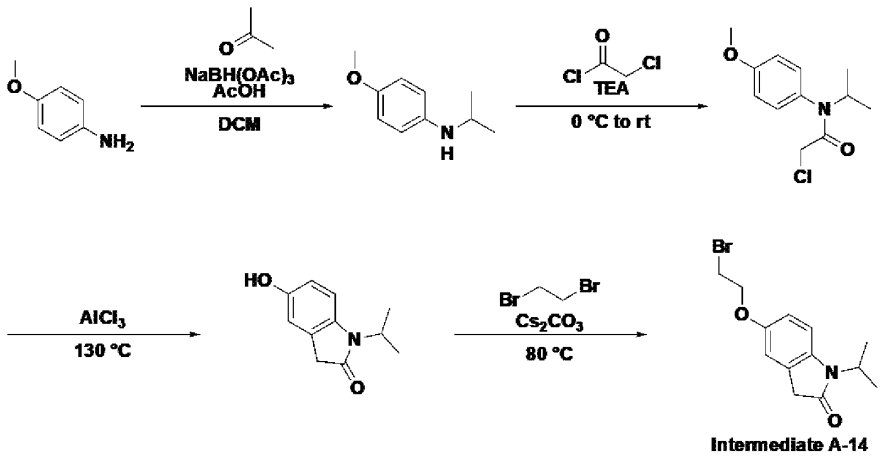
[0623] A mixture of 4-bromo-3-(difluoromethyl)phenol (3.60 g, 16.1 mmol), sodium methanesulfinate (16.5 g, 161 mmol), NaOH (323 mg, 8.07 mmol), (2*S*)-pyrrolidine-2-carboxylic acid (929 mg, 8.07 mmol) and copper(I) iodide (3.07 g, 16.1 mmol) in DMSO (40 mL) was degassed and purged with N_2 (3x). The mixture was stirred at 100 °C for 48 h. The reaction mixture was poured into ice water (200 mL) and then extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine (2 x 300 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 80 g cartridge, 0–30% EtOAc:petroleum ether) to give 3-(difluoromethyl)-4-methanesulfonylphenol (**Intermediate A-12**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.04 (s, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.67–7.40 (m, 1H), 7.20 (s, 1H), 7.11 (d, J = 4.2 Hz, 1H), 3.21 (s, 3H).

Step 3: 4-(2-bromoethoxy)-2-(difluoromethyl)-1-methanesulfonylbenzene

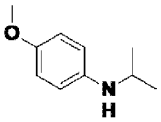


[0624] To a solution of 3-(difluoromethyl)-4-methanesulfonylphenol (300 mg, 1.35 mmol) in 1, 2-dibromoethane (7.5 mL) was added Cs_2CO_3 (1.32 g, 4.05 mmol). The mixture was stirred at 100 °C for 12 h. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 0–30% EtOAc:petroleum ether) to give 4-(2-bromoethoxy)-2-(difluoromethyl)-1-methanesulfonylbenzene (**Intermediate A-13**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99 (d, J = 8.8 Hz, 1H), 7.74–7.55 (m, 1H), 7.47–7.32 (m, 2H), 4.56–4.49 (m, 2H), 3.87–3.82 (m, 2H), 3.26 (s, 3H).

General Procedure for Intermediate A-14



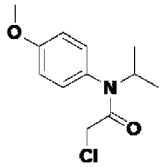
Step 1: 4-methoxy-*N*-(propan-2-yl)aniline



[0625] To a solution of 4-methoxyaniline (500 mg, 4.06 mmol) in DCM (10 mL) was added dropwise acetone (943 mg, 16.2 mmol) and AcOH (975 mg, 16.2 mmol). The mixture was stirred at room temperature for 1 h, and then $NaBH(OAc)_3$ (1.08 g, 5.08 mmol) was added. The resulting

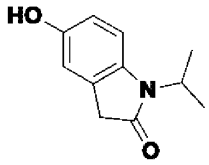
mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–30% EtOAc:petroleum ether) to give 4-methoxy-N-(propan-2-yl)aniline. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.72–6.61 (m, 2H), 6.54–6.45 (m, 2H), 4.81 (s, 1H), 3.62 (s, 3H), 3.49–3.39 (m, 1H), 1.08 (d, J = 6.4 Hz, 6H). MS = 166.2 $[M+H]^+$.

Step 2: 2-chloro-N-(4-methoxyphenyl)-*N*-(propan-2-yl)acetamide



[0626] A mixture of 4-methoxy-N-(propan-2-yl)aniline (200 mg, 1.21 mmol), TEA (253 µL, 1.82 mmol) in DCM (3 mL) was degassed and purged with N_2 (3x). The mixture was cooled to 0 °C and 2-chloroacetyl chloride (273 mg, 2.42 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 12 h under N_2 atmosphere. The reaction mixture was quenched with H_2O (15 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 ml) followed by brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Isco 4 g cartridge, 0–40% EtOAc:petroleum ether) to give 2-chloro-N-(4-methoxyphenyl)-N-(propan-2-yl)acetamide. MS = 242.1 $[M+H]^+$.

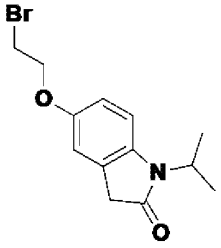
Step 3: 5-hydroxy-1-(propan-2-yl)-2,3-dihydro-1H-indol-2-one



[0627] To 2-chloro-N-(4-methoxyphenyl)-N-(propan-2-yl)acetamide (1.00 g, 4.14 mmol) was slowly added aluminum chloride (2.21 g, 16.6 mmol). The mixture was stirred at 130 °C for 3 h. After cooling to room temperature, the reaction mixture was quenched with aqueous 1.0 M NaOH (20 mL), diluted with H_2O (10 mL), and extracted with EtOAc (3 x 30 mL). The combined organic

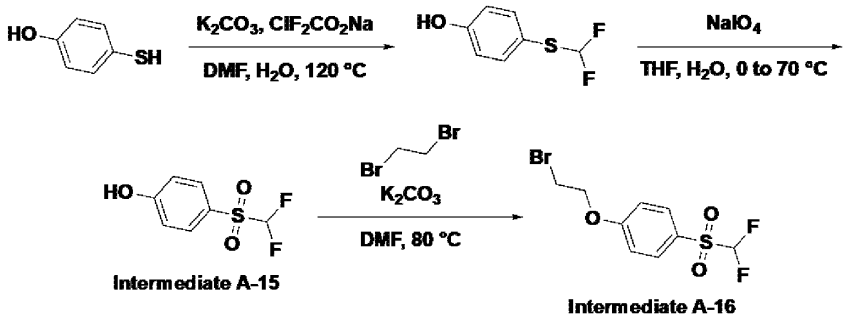
layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Isco 12 g cartridge, 0–40% EtOAc:petroleum ether) to give 5-hydroxy-1-(propan-2-yl)-2,3-dihydro-1H-indol-2-one. MS = 192.2 $[M+H]^+$.

Step 4: 5-(2-bromoethoxy)-1-(propan-2-yl)-2,3-dihydro-1H-indol-2-one

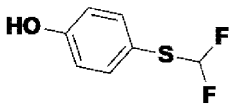


[0628] To a solution of 5-hydroxy-1-(propan-2-yl)-2,3-dihydro-1H-indol-2-one (500 mg, 2.61 mmol) in 1,2-dibromoethane (8 mL) was added Cs_2CO_3 (2.56 g, 7.84 mmol). The mixture was stirred at 80 °C for 12 h. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Isco 12 g cartridge, 0–60% EtOAc:petroleum ether) to give 5-(2-bromoethoxy)-1-(propan-2-yl)-2,3-dihydro-1H-indol-2-one (**Intermediate A-14**). MS = 298.1 / 300.1 $[M+H]^+$.

General Procedure for Intermediates A-15 & A-16

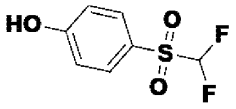


Step 1: 4-[(difluoromethyl)sulfanyl]phenol



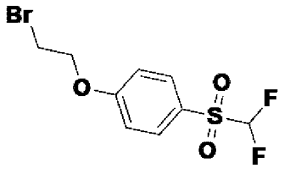
[0629] To a solution of 4-sulfanylphenol (300 mg, 2.38 mmol) in DMF (4 mL) and H_2O (1 mL) were added K_2CO_3 (1.97 g, 14.3 mmol) and 2-chloro-2,2-difluoro-acetic acid (302 µL, 3.57 mmol). The mixture was stirred at 120 °C for 15 h. After cooling to room temperature, the reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–30% EtOAc:petroleum ether) to give 4-[(difluoromethyl)sulfanyl]phenol. MS = 177.0 $[M+H]^+$.

Step 2: 4-difluoromethanesulfonylphenol



[0630] To a 0 °C solution of 4-[(difluoromethyl)sulfanyl]phenol (100 mg, 0.568 mmol) in THF (1 mL) and H_2O (1 mL) was added $NaIO_4$ (94.4 µL, 1.70 mmol). The mixture was stirred at 70 °C for 15 h. After cooling to room temperature, the reaction mixture was quenched by the addition of saturated aqueous Na_2SO_3 (20 mL), and then extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 4 g cartridge, 0–30% EtOAc:petroleum ether) to give 4-difluoromethanesulfonylphenol **(Intermediate A-15)**. MS = 207.0 $[M–H]^+$.

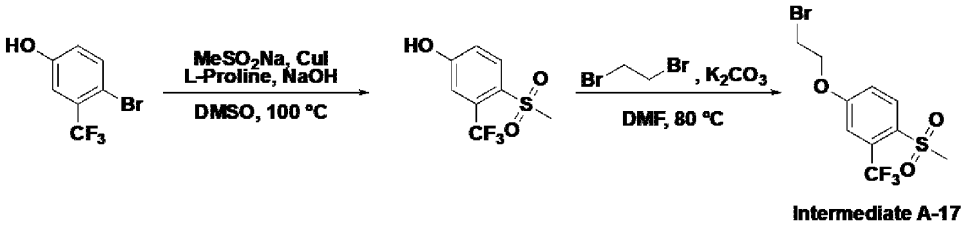
Step 3: 1-(2-bromoethoxy)-4-difluoromethanesulfonylbenzene



[0631] To a mixture of 4-(difluoromethylsulfonyl)phenol (500 mg, 2.40 mmol) and 1,2-dibromoethane (906 µL, 12.0 mmol) in DMF (5 mL) was added K_2CO_3 (664 mg, 4.80 mmol). The mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (20 mL), and then extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–50% EtOAc:petroleum ether) to give 1-(2-bromoethoxy)-4-difluoromethanesulfonylbenzene

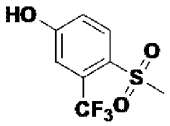
(Intermediate A-16). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.80 (d, J = 2.8 Hz, 2H), 7.21–7.04 (m, 3H), 4.95 (t, J = 7.2 Hz, 2H), 3.85 (t, J = 7.2 Hz, 2H).

General Procedure for Intermediate A-17



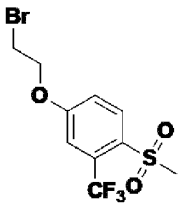
Intermediate A-17

Step 1: 4-methanesulfonyl-3-(trifluoromethyl)phenol



[0632] A mixture of 4-bromo-3-(trifluoromethyl)phenol (7.00 g, 29.1 mmol), sodium methanesulfinate (29.7 g, 290 mmol), CuI (2.77 g, 14.5 mmol), NaOH (581 mg, 14.5 mmol) and L-Proline (1.67 g, 14.5 mmol) in DMSO (100 mL) was degassed and purged with N_2 (3x). The mixture was stirred at 100 °C for 3 d under N_2 atmosphere. After cooling to room temperature, the reaction mixture was quenched with H_2O (80 mL) and extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 80 g cartridge, 0–50% EtOAc:petroleum ether) to give 4-methanesulfonyl-3-(trifluoromethyl)phenol. MS = 239.1 $[M–H]^-$.

Step 2: 4-(2-bromoethoxy)-1-methanesulfonyl-2-(trifluoromethyl)benzene



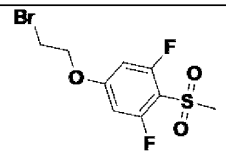
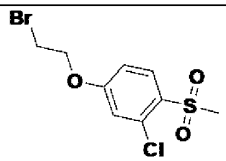
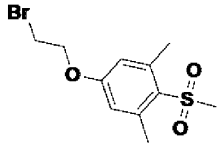
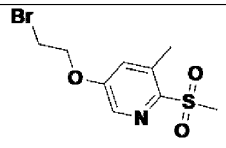
[0633] To a solution of 4-methylsulfonyl-3-(trifluoromethyl)phenol (500 mg, 2.08 mmol) in DMF (5 mL) were added 1,2-dibromoethane (2.36 mL, 31.2 mmol) and K_2CO_3 (575 mg, 4.16 mmol). The mixture was stirred at 80 °C for 2 h. After cooling to room temperature, the reaction

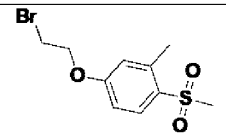
mixture was quenched with H_2O (8 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–25% EtOAc:petroleum ether) to give 4-(2-bromoethoxy)-1-methanesulfonyl-2-(trifluoromethyl)benzene (**Intermediate A-17**). MS = 347.0 / 349.0 $[M+H]^+$.

[0634] The following intermediates in Table 4 were prepared according to procedures similar those described for **Intermediate A-17** using the appropriate starting materials.

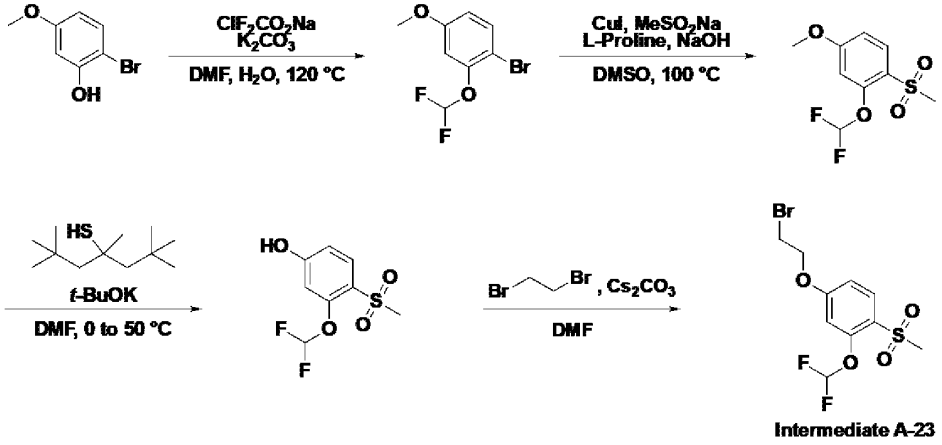
General Procedure for Intermediates A-18 to A-22

Table 4.

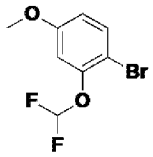
Intermediate #	Structure	Name	Exact Mass $[M+H]^+$
A-18		5-(2-bromoethoxy)-1,3-difluoro-2-methanesulfonylbenzene	Calc'd 332.0 / 334.0 Found 332.1 / 334.0 $[M+NH_4]^+$
A-19		4-(2-bromoethoxy)-2-chloro-1-methanesulfonylbenzene	Calc'd 312.9 / 314.9 Found 312.9 / 315.0
A-20		5-(2-bromoethoxy)-2-methanesulfonyl-1,3-dimethylbenzene	Calc'd 307.0 / 309.0 Found 307.1 / 309.0
A-21		5-(2-bromoethoxy)-2-methanesulfonyl-3-methylpyridine	Calc'd 294.0 / 296.0 Found 294.0 / 296.0

A-22		4-(2-bromoethoxy)-1-methanesulfonyl-2-methylbenzene	Calc'd 293.0 / 295.0 Found 293.0 / 295.0

General Procedure for Intermediate A-23

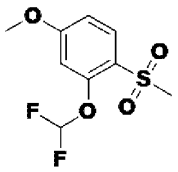


Step 1: 1-bromo-2-(difluoromethoxy)-4-methoxybenzene



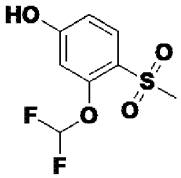
[0635] To a solution of 2-bromo-5-methoxyphenol (2.50 g, 12.3 mmol) in DMF (36 mL) and H_2O (9 mL) were added K_2CO_3 (10.2 g, 73.9 mmol) and sodium chlorodifluoroacetate (4.69 g, 30.8 mmol). The mixture was stirred at 120 °C for 15 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Isco 40 g cartridge, 0–7% EtOAc:petroleum ether) to give 1-bromo-2-(difluoromethoxy)-4-methoxybenzene.

Step 2: 2-(difluoromethoxy)-1-methanesulfonyl-4-methoxybenzene



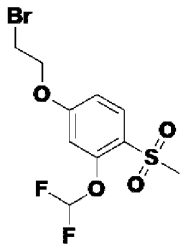
[0636] A mixture of 1-bromo-2-(difluoromethoxy)-4-methoxybenzene (3.00 g, 11.9 mmol), sodium methanesulfinate (6.05 g, 59.3 mmol), L-Proline (409 mg, 3.56 mmol), sodium hydroxide (142 mg, 3.56 mmol) and copper (I) iodide (1.13 g, 5.93 mmol) in DMSO (30 mL) was degassed and purged with N_2 (3x). The mixture was stirred at 100 °C for 12 h under N_2 atmosphere. After cooling to room temperature, the reaction mixture was quenched with H_2O (80 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Isco 80 g cartridge, 0–23% EtOAc:petroleum ether) to give 2-(difluoromethoxy)-1-methanesulfonyl-4-methoxybenzene. MS = 253.2 $[M+H]^+$.

Step 3: 3-(difluoromethoxy)-4-methanesulfonylphenol



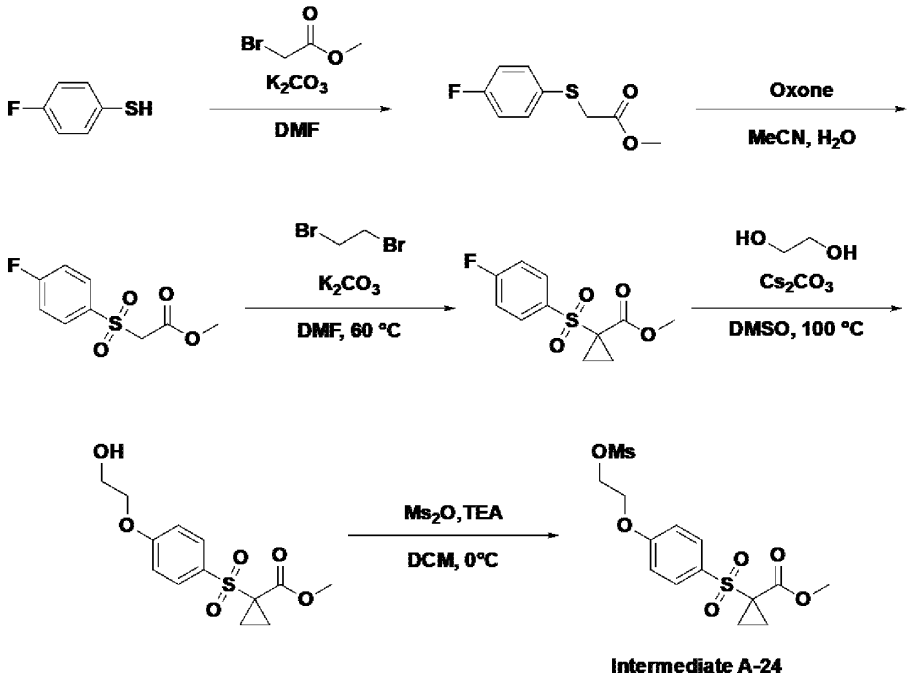
[0637] A mixture of 2,2,4,6,6-pentamethylheptane-4-thiol (2.70 g, 13.3 mmol) and *t*-BuOK (1.56 g, 13.9 mmol) in DMF (14 mL) was degassed and purged with N_2 (3x). The mixture was cooled to 0 °C and a solution of 2-(difluoromethoxy)-1-methanesulfonyl-4-methoxybenzene (1.4 g, 5.55 mmol) in DMF (14 mL) was added dropwise. The resulting mixture was stirred at 50 °C for 2 h. After cooling to room temperature, the reaction mixture was quenched with H_2O (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Isco 40 g cartridge, 0–33% EtOAc:petroleum ether) to give 3-(difluoromethoxy)-4-methanesulfonylphenol. MS = 239.2 $[M+H]^+$.

Step 4: 4-(2-bromoethoxy)-2-(difluoromethoxy)-1-methanesulfonylbenzene



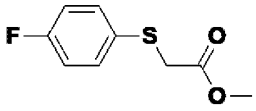
[0638] To a mixture of 3-(difluoromethoxy)-4-methanesulfonylphenol (370 mg, 1.55 mmol) and 1,2-dibromoethane (3.00 mL, 39.7 mmol) in DMF (3 mL) was added Cs_2CO_3 (1.01 g, 3.11 mmol). After stirring at room temperature for 12 h, the mixture was diluted with H_2O (15 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Isco 4 g cartridge, 0–30% EtOAc:petroleum ether) to give 4-(2-bromoethoxy)-2-(difluoromethoxy)-1-methanesulfonylbenzene (**Intermediate A-23**). MS = 362.1 / 364.0 $[M+NH_4]^+$.

General Procedure for Intermediate A-24



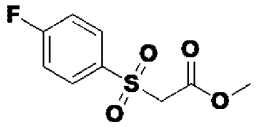
Intermediate A-24

Step 1: methyl 2-[(4-fluorophenyl)sulfanyl]acetate



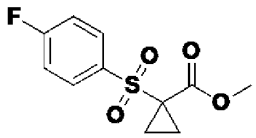
[0639] To a solution of 4-fluorobenzene-1-thiol (1.25 mL, 11.7 mmol) in DMF (15 mL) were added K_2CO_3 (3.23 g, 23.4 mmol) and methyl 2-bromoacetate (1.33 mL, 14.0 mmol). The mixture was stirred at room temperature for 5 h. After cooling to 0 °C, the reaction mixture was quenched with H_2O (15 mL) and extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 25 g cartridge, 1–20% EtOAc:petroleum ether) to give methyl 2-[(4-fluorophenyl)sulfanyl]acetate. MS = 201.0 $[M+H]^+$.

Step 2: methyl 2-(4-fluorobenzenesulfonyl)acetate



[0640] To a solution of methyl 2-[(4-fluorophenyl)sulfanyl]acetate (2.20 g, 11.0 mmol) in MeCN (30 mL) and H_2O (3 mL) was added Oxone (8.11 g, 13.2 mmol). After stirring at room temperature for 16 h, the mixture cooled to 0 °C and quenched with saturated aqueous $Na_2S_2O_3$ (40 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 25 g cartridge, 15–45% EtOAc:petroleum ether) to give methyl 2-(4-fluorobenzenesulfonyl)acetate. MS = 233.0 $[M+H]^+$.

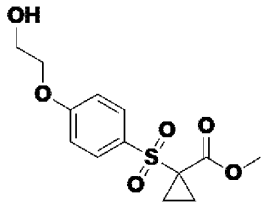
Step 3: methyl 1-(4-fluorobenzenesulfonyl)cyclopropane-1-carboxylate



[0641] To a solution of methyl 2-(4-fluorobenzenesulfonyl)acetate (1.10 g, 4.74 mmol) in DMF (10 mL) were added K_2CO_3 (1.64 g, 11.8 mmol) and 1,2-dibromoethane (429 µL, 5.68 mmol). The mixture was stirred at 60 °C for 6 h. The reaction mixture was cooled to 0 °C, quenched with H_2O (20 mL), and extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with

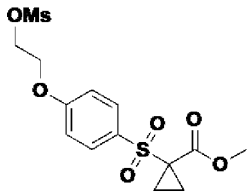
brine (2 x 15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 15–45% EtOAc:petroleum ether) to give methyl 1-(4-fluorobenzenesulfonyl)cyclopropane-1-carboxylate. MS = 259.0 $[M+H]^+$.

Step 4: methyl 1-[4-(2-hydroxyethoxy)benzenesulfonyl]cyclopropane-1-carboxylate



[0642] To a solution of methyl 1-(4-fluorobenzenesulfonyl)cyclopropane-1-carboxylate (1.50 g, 5.81 mmol) in DMSO (15 mL) were added Cs_2CO_3 (5.68 g, 17.4 mmol) and ethylene glycol (6.50 mL, 116 mmol). The mixture was stirred at 100 °C for 5 h. The hydrolysis product of the ester was detected. After cooling to room temperature, MeI (1.08 mL, 17.4 mmol) was added to the mixture. The reaction mixture was stirred at room temperature for 1 h and was then quenched with H_2O (30 mL) and extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 45–80% EtOAc:petroleum ether) to give methyl 1-[4-(2-hydroxyethoxy)benzenesulfonyl]cyclopropane-1-carboxylate. MS = 301.1 $[M+H]^+$.

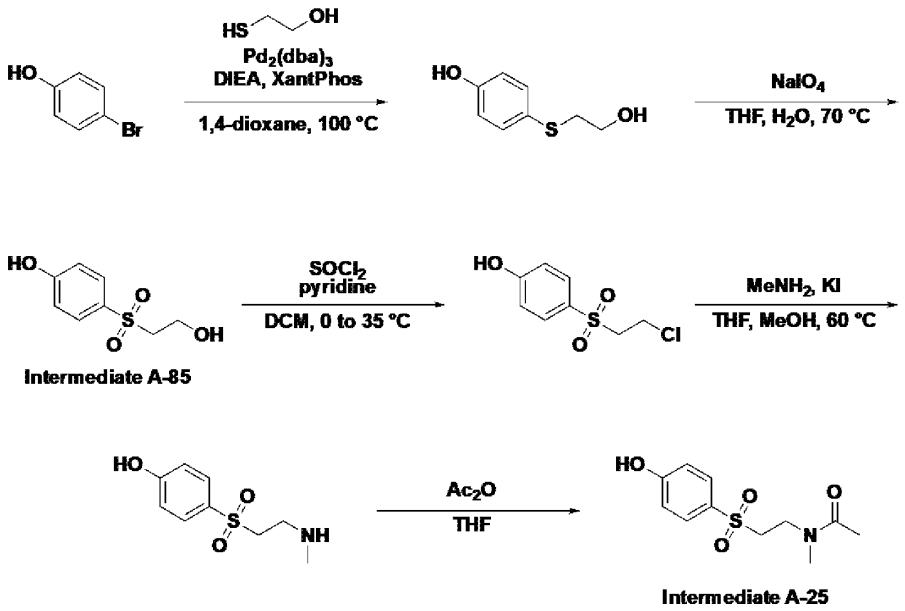
Step 5: methyl 1-{4-[2-(methanesulfonyloxy)ethoxy]benzenesulfonyl}cyclopropane-1-carboxylate



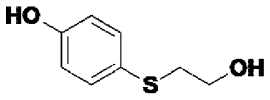
[0643] To a 0 °C solution of methyl 1-[4-(2-hydroxyethoxy)benzenesulfonyl]cyclopropane-1-carboxylate (570 mg, 1.90 mmol) in DCM (10 mL) were added TEA (528 µL, 3.80 mmol) and methylsulfonyl methanesulfonate (397 mg, 2.28 mmol). The mixture was stirred at 0 °C for 3 h, and then quenched with H_2O (10 mL). 4 M aqueous HCl (0.1 mL) was added, and the mixture was

extracted with EtOAc (8 mL x 2). The combined organic layers were washed with brine (2 x 8 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give methyl 1-{4-[2-(methanesulfonyloxy)ethoxy]benzenesulfonyl}cyclopropane-1-carboxylate (**Intermediate A-24**), which was used in the subsequent step without further purification. MS = 378.9 $[M+H]^+$.

General Procedure for Intermediates A-25 & A-85

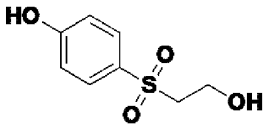


Step 1: 4-[(2-hydroxyethyl)sulfanyl]phenol



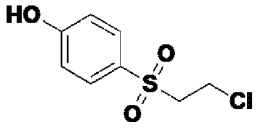
[0644] A solution of 4-bromophenol (10.0 g, 57.8 mmol), 2-sulfanylethanol (5.24 mL, 75.1 mmol), XantPhos (6.69 g, 11.6 mmol), $Pd_2(dba)_3$ (5.29 g, 5.78 mmol) and DIEA (25.2 mL, 145 mmol) in 1,4-dioxane (10 mL) was degassed and purged with N_2 (3x). The mixture was stirred at 100 °C for 12 h under N_2 atmosphere. After cooling to room temperature, the reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 0–50% EtOAc:petroleum ether) to give 4-[(2-hydroxyethyl)sulfanyl]phenol.

Step 2: 4-(2-hydroxyethanesulfonyl)phenol



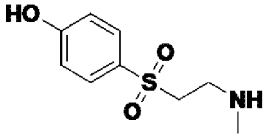
[0645] A solution of 4-[(2-hydroxyethyl)sulfanyl]phenol (4.80 g, 28.2 mmol), $NaIO_4$ (4.69 mL, 84.6 mmol) in THF (50 mL) and H_2O (50 mL) was degassed and purged with N_2 (3x). The mixture was stirred at 70 °C for 12 h under N_2 atmosphere. After cooling to room temperature, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (100 mL) and extracted with EtOAc (2 x 70 mL). The combined organic layers were washed with brine (70 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give 4-(2-hydroxyethanesulfonyl)phenol (**Intermediate A-85**), which was used in the subsequent step without further purification. MS = 203.0 $[M+H]^+$.

Step 3: 4-(2-chloroethanesulfonyl)phenol



[0646] To a 0 °C mixture of 4-(2-hydroxyethanesulfonyl)phenol (600 mg, 2.97 mmol) and pyridine (478 µL, 5.93 mmol) in DCM (6 mL) was added $SOCl_2$ (645 µL, 8.90 mmol). The mixture was stirred at 35 °C for 16 h. After cooling to room temperature, the reaction mixture was quenched with H_2O (20 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–100% EtOAc:petroleum ether) to give 4-(2-chloroethanesulfonyl)phenol.

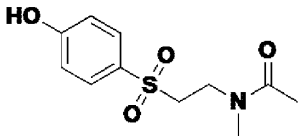
Step 4: 4-[2-(methylamino)ethanesulfonyl]phenol



[0647] A mixture of 4-(2-chloroethanesulfonyl)phenol (250 mg, 1.13 mmol), 2.0 M methylamine in MeOH (7.93 mL, 15.9 mmol), and KI (75 mg, 0.45 mmol) in THF (2 mL) was stirred at 60 °C for 16 h under N_2 atmosphere. After cooling to room temperature, the mixture was filtered, and the filtrate was concentrated in vacuo to give 4-[2-

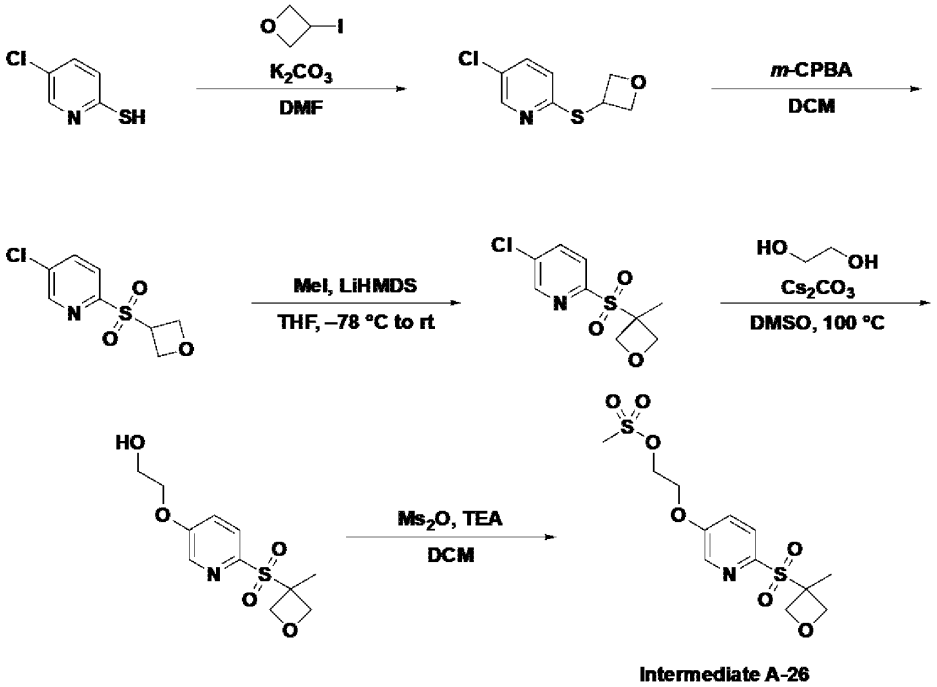
(methylamino)ethanesulfonyl]phenol, which was used in the subsequent step without further purification. MS = 216.1 $[M+H]^+$.

Step 5: *N*-[2-(4-hydroxybenzenesulfonyl)ethyl]-N-methylacetamide



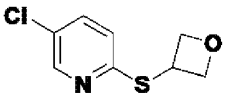
[0648] A mixture of 4-[2-(methylamino)ethanesulfonyl]phenol (340 mg, 1.58 mmol) and Ac2O (147 µL, 1.58 mmol) in THF (5 mL) was stirred for 16 h. The mixture was filtered and the filtered cake was concentrated under in vacuo to give N-[2-(4-hydroxybenzenesulfonyl)ethyl]-N-methylacetamide (**Intermediate A-25**), which was used in the subsequent step without further purification. MS = 258.2 $[M+H]^+$.

General Procedure for Intermediate A-26



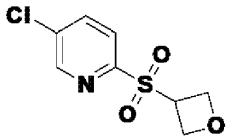
Intermediate A-26

Step 1: 5-chloro-2-(oxetan-3-ylsulfanyl)pyridine



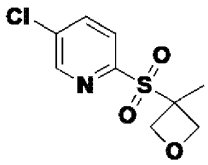
[0649] To a solution of 5-chloropyridine-2-thiol (4.50 g, 30.9 mmol) in DMF (50 mL) were added K_2CO_3 (8.54 g, 61.8 mmol) and 3-iodooxetane (6.82 g, 37.1 mmol). The mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with H_2O (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 80 g cartridge, 0–15% EtOAc:petroleum ether) to give 5-chloro-2-(oxetan-3-ylsulfanyl)pyridine. MS = 202.0 $[M+H]^+$.

Step 2: 5-chloro-2-(oxetane-3-sulfonyl)pyridine



[0650] To a 0 °C solution of 5-chloro-2-(oxetan-3-ylsulfanyl)pyridine (3.00 g, 14.9 mmol) in DCM (40 mL) was added m-CPBA (6.04 g, 85% purity, 29.8 mmol). The mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with saturated aqueous Na_2SO_3 (20 mL), diluted with H_2O (100 mL), and extracted with DCM (3 x 50 mL). The combined organic layers were washed with saturated aqueous Na_2SO_3 (2 x 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was triturated with EtOAc (5 mL) and isolated by filtration to give 5-chloro-2-(oxetane-3-sulfonyl)pyridine. MS = 234.0 $[M+H]^+$.

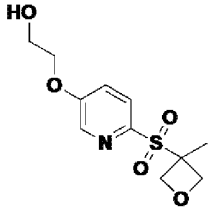
Step 3: 5-chloro-2-[(3-methyloxetan-3-yl)sulfonyl]pyridine



[0651] To a –78 °C solution of 5-chloro-2-(oxetane-3-sulfonyl)pyridine (500 mg, 2.14 mmol) in THF (8 mL) was added 1.0 M LiHMDS in THF (4.28 mL, 4.28 mmol). After stirring for 30 min, MeI (160 µL, 2.57 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 30 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by

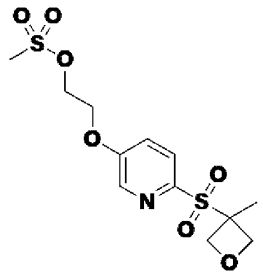
normal phase silica gel chromatography (Biotage 12 g cartridge, 0–15% EtOAc:petroleum ether) to give 5-chloro-2-[(3-methyloxetan-3-yl)sulfonyl]pyridine. MS = 248.0 $[M+H]^+$.

Step 4: 2-({6-[(3-methyloxetan-3-yl)sulfonyl]pyridin-3-yl}oxy)ethan-1-ol



[0652] To a solution of 5-chloro-2-[(3-methyloxetan-3-yl)sulfonyl]pyridine (350 mg, 1.41 mmol) in DMSO (2 mL) were added ethylene glycol (2.00 mL, 35.8 mmol) and Cs_2CO_3 (921 mg, 2.83 mmol). The mixture was stirred at 100 °C for 7 h. After cooling to 0 °C, the reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (6 x 10 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 4 g cartridge, 0–70% EtOAc:petroleum ether) to give 2-({6-[(3-methyloxetan-3-yl)sulfonyl]pyridin-3-yl}oxy)ethan-1-ol. MS = 274.1 $[M+H]^+$.

Step 5: 2-({6-[(3-methyloxetan-3-yl)sulfonyl]pyridin-3-yl}oxy)ethyl methanesulfonate

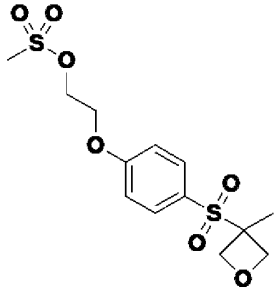


[0653] To a solution of 2-({6-[(3-methyloxetan-3-yl)sulfonyl]pyridin-3-yl}oxy)ethan-1-ol (130 mg, 0.476 mmol) in DCM (3 mL) was added TEA (199 µL, 1.43 mmol) and methanesulfonic anhydride (166 mg, 0.951 mmol). The mixture was stirred at room temperature for 5 h, and then diluted with H_2O (10 mL) and extracted with DCM (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give 2-({6-[(3-methyloxetan-3-yl)sulfonyl]pyridin-3-yl}oxy)ethyl methanesulfonate (**Intermediate A-26**), which was used in the subsequent step without further purification. MS = 352.1 $[M+H]^+$.

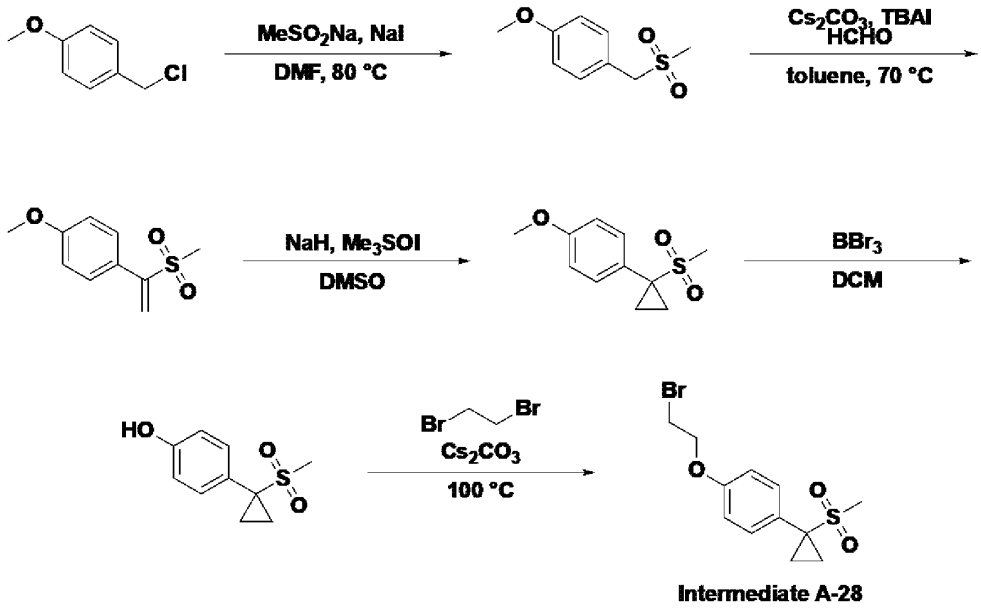
[0654] The following intermediate in Table 5 was prepared using procedures similar to those described for **Intermediate A-26**, using the appropriate starting materials.

General Procedure for Intermediate A-27

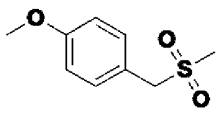
Table 5.

Intermediate #	Structure	Name	Exact Mass $[M+H]^+$
A-27		2-{4-[(3-methyloxetan-3-yl)sulfonyl]phenoxy}ethyl methanesulfonatele	Calc'd 351.1 Found 350.9

General Procedure for Intermediate A-28

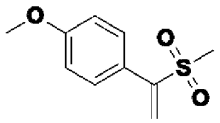


Step 1: 1-(methanesulfonylmethyl)-4-methoxybenzene



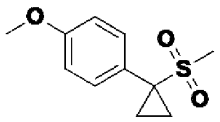
[0655] A mixture of 1-(chloromethyl)-4-methoxybenzene (8.70 mL, 63.9 mmol), sodium methanesulfinate (9.13 g, 89.4 mmol) and NaI (28.7 mg, 0.192 mmol) in DMF (80 mL) was stirred at 80 °C for 3 h. After cooling to 0 °C, the reaction mixture was quenched with H_2O (200 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was triturated with EtOAc (50 mL) to give 1-(methanesulfonylmethyl)-4-methoxybenzene, which was used in the subsequent step without further purification.

Step 2: 1-(1-methanesulfonylethenyl)-4-methoxybenzene



[0656] A mixture of 1-(methanesulfonylmethyl)-4-methoxybenzene (9.00 g, 44.9 mmol), Cs_2CO_3 (43.9 g, 135 mmol), TBAI (166 mg, 0.449 mmol) and HCHO (12.4 mL, 449 mmol) in toluene (150 mL) was stirred at 70 °C for 3 h. After cooling to 0 °C, the reaction mixture was quenched with H_2O (200 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 120 g cartridge, 0–30% EtOAc:petroleum ether) to give 1-(1-methanesulfonylethenyl)-4-methoxybenzene. MS = 213.1 $[M+H]^+$.

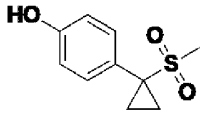
Step 3: 1-(1-methanesulfonylcyclopropyl)-4-methoxybenzene



[0657] To a solution of trimethylsulfoxonium iodide (523 mg, 2.37 mmol) in DMSO (5 mL) was added NaH (84.4 mg, 60 wt% in mineral oil, 2.11 mmol). After stirring at room temperature for 1 h, 1-(1-methanesulfonylethenyl)-4-methoxybenzene (0.28 g, 1.32 mmol) was added. The mixture was stirred for 16 h, then cooled to 0 °C, quenched with saturated aqueous NH_4Cl (10 mL), and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by

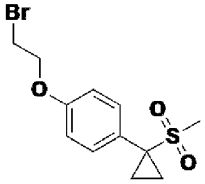
normal phase silica gel chromatography (Biotage 4 g cartridge, 0–50% EtOAc:petroleum ether) to give 1-(1-methanesulfonylcyclopropyl)-4-methoxybenzene. MS = 244.2 $[M+NH_4]^+$.

Step 4: 4-(1-methanesulfonylcyclopropyl)phenol



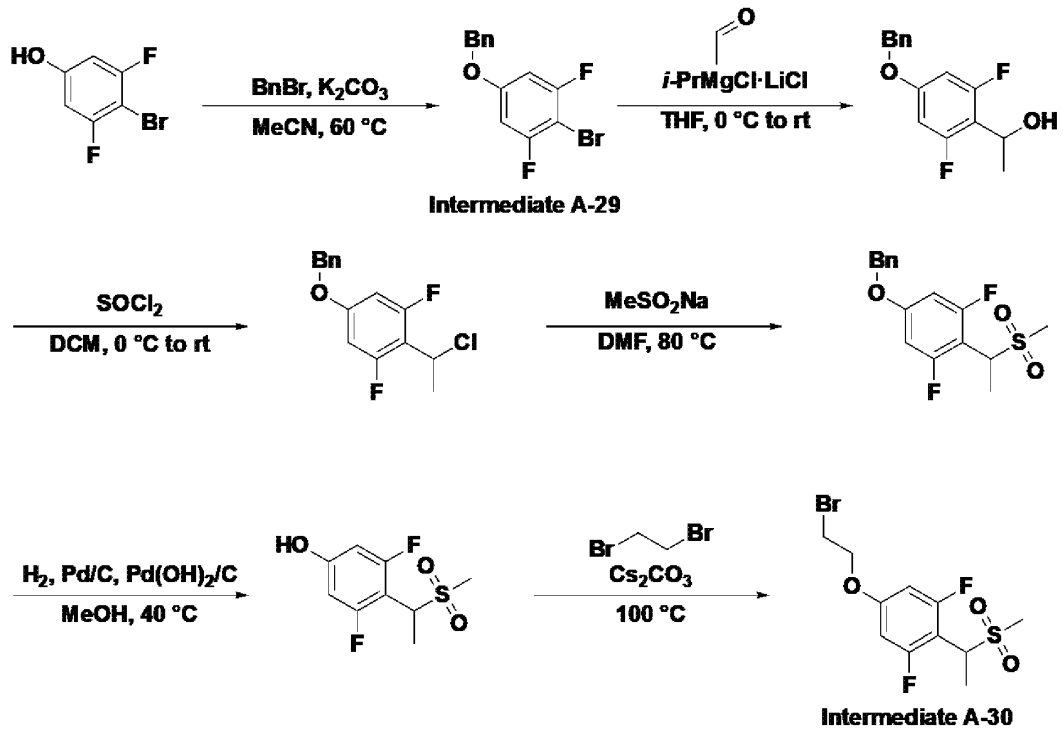
[0658] To a 0 °C solution of 1-(1-methanesulfonylcyclopropyl)-4-methoxybenzene (1.20 g, 5.30 mmol) in DCM (20 mL) was added BBr_3 (1.53 mL, 15.9 mmol). The mixture was allowed to warm to room temperature and stirred for 3 h. After cooling to 0 °C, the reaction mixture was quenched with H_2O (30 mL). The pH of the 0 °C solution was adjusted to pH = 7 with the dropwise addition of saturated aqueous $NaHCO_3$. The biphasic mixture was extracted with DCM (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give 4-(1-methanesulfonylcyclopropyl)phenol, which was used in the subsequent step without further purification.

Step 5: 1-(2-bromoethoxy)-4-(1-methanesulfonylcyclopropyl)benzene

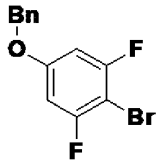


[0659] To a solution of 4-(1-methanesulfonylcyclopropyl)phenol (200 mg, 0.942 mmol) in 1,2-dibromoethane (4.27 mL, 56.5 mmol) was added Cs_2CO_3 (614 mg, 1.88 mmol). The mixture was stirred at 100 °C for 4 h. After cooling to room temperature, the reaction mixture was quenched with H_2O (10 mL) and extracted with DCM (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 4 g cartridge, 0–30% EtOAc:petroleum ether) to give 1-(2-bromoethoxy)-4-(1-methanesulfonylcyclopropyl)benzene (**Intermediate A-28**). MS = 336.0 / 338.1 $[M+NH_4]^+$.

General Procedure for Intermediates A-29 & A-30

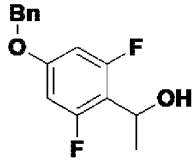


Step 1: 5-(benzyloxy)-2-bromo-1,3-difluorobenzene



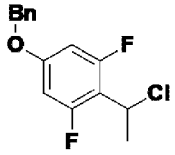
[0660] To a solution of 4-bromo-3,5-difluorophenol (10.0 g, 47.8 mmol) in MeCN (100 mL) were added BnBr (6.82 mL, 57.4 mmol) and K_2CO_3 (19.8 g, 144 mmol). The mixture was stirred at 60 °C for 12 h. After cooling to room temperature, the mixture was poured into saturated aqueous $NaHCO_3$ (400 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (2 x 200 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 80 g cartridge, 0–1% EtOAc:petroleum ether) to give 5-(benzyloxy)-2-bromo-1,3-difluorobenzene (**Intermediate A-29**). ^1H NMR (400 MHz, $CDCl_3$): δ 7.42–7.35 (m, 5H), 6.64–6.60 (m, 2H), 5.04 (s, 2H).

Step 2: 1-[4-(benzyloxy)-2,6-difluorophenyl]ethan-1-ol



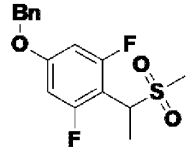
[0661] To a 0 °C solution of 5-(benzyloxy)-2-bromo-1,3-difluorobenzene (12.0 g, 40.1 mmol) in THF (24 mL) was added 1.3 M *i*-PrMgCl•LiCl in THF (34.0 mL, 44.1 mmol). The mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was cooled to 0 °C and 5.0 M acetaldehyde in THF (8.82 mL, 44.1 mmol) was added into the reaction mixture. After stirring at 0 °C for 30 min, the mixture was warmed to room temperature and stirred for another 30 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (300 mL) and extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with brine (2 x 300 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 80 g cartridge, 0–35% EtOAc:petroleum ether) to give 1-[4-(benzyloxy)-2,6-difluorophenyl]ethan-1-ol. MS = 247.2 $[M–OH]^+$.

Step 3: 5-(benzyloxy)-2-(1-chloroethyl)-1,3-difluorobenzene



[0662] To a 0 °C solution of 1-[4-(benzyloxy)-2,6-difluorophenyl]ethan-1-ol (5.8 g, 21.9 mmol) in DCM (60 mL) was added $SOCl_2$ (3.18 mL, 43.9 mmol). The mixture was stirred at room temperature for 4 h, and then concentrated in vacuo to give 5-(benzyloxy)-2-(1-chloroethyl)-1,3-difluorobenzene, which was used in the subsequent step without further purification.

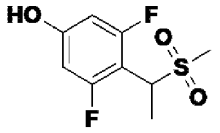
Step 4: 5-(benzyloxy)-1,3-difluoro-2-(1-methanesulfonylethyl)benzene



[0663] To a solution of 5-(benzyloxy)-2-(1-chloroethyl)-1,3-difluorobenzene (6.20 g, 21.9 mmol) in DMF (60 mL) was added sodium methanesulfinate (4.48 g, 43.9 mmol). The mixture was stirred at 80 °C for 12 h. After cooling to room temperature, the reaction mixture was quenched with

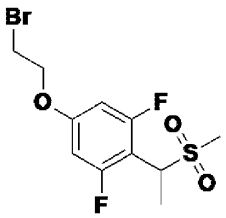
H_2O (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 80 g cartridge, 0–50% EtOAc:petroleum ether) to give 5-(benzyloxy)-1,3-difluoro-2-(1-methanesulfonylethyl)benzene.

Step 5: 3,5-difluoro-4-(1-methanesulfonylethyl)phenol



[0664] To a solution of 5-(benzyloxy)-1,3-difluoro-2-(1-methanesulfonylethyl)benzene (3.00 g, 9.19 mmol) in MeOH (30 mL) was added Pd/C (0.50 g, 10 wt%, 0.47 mmol) and $Pd(OH)_2/C$ (0.50 g, 20 wt%, 0.70 mmol). The mixture was stirred at 40 °C for 16 h under an atmosphere of H_2 (50 psi). After cooling to room temperature, the reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 80 g cartridge, 0–100% EtOAc:petroleum ether) to give 3,5-difluoro-4-(1-methanesulfonylethyl)phenol. MS = 254.1 $[M+NH_4]^+$.

Step 6: 5-(2-bromoethoxy)-1,3-difluoro-2-(1-methanesulfonylethyl)benzene

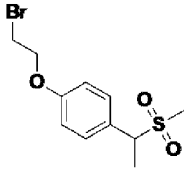


[0665] To a solution of 3,5-difluoro-4-(1-methanesulfonylethyl)phenol (0.43 g, 1.82 mmol) in 1,2-dibromoethane (10 mL, 132 mmol) was added Cs_2CO_3 (1.19 g, 3.64 mmol). The mixture was stirred at 100 °C for 12 h. After cooling to room temperature, the reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 0–50% EtOAc:petroleum ether) to give 5-(2-bromoethoxy)-1,3-difluoro-2-(1-methanesulfonylethyl)benzene (**Intermediate A-30**). MS = 360.1 / 362.1 $[M+NH_4]^+$.

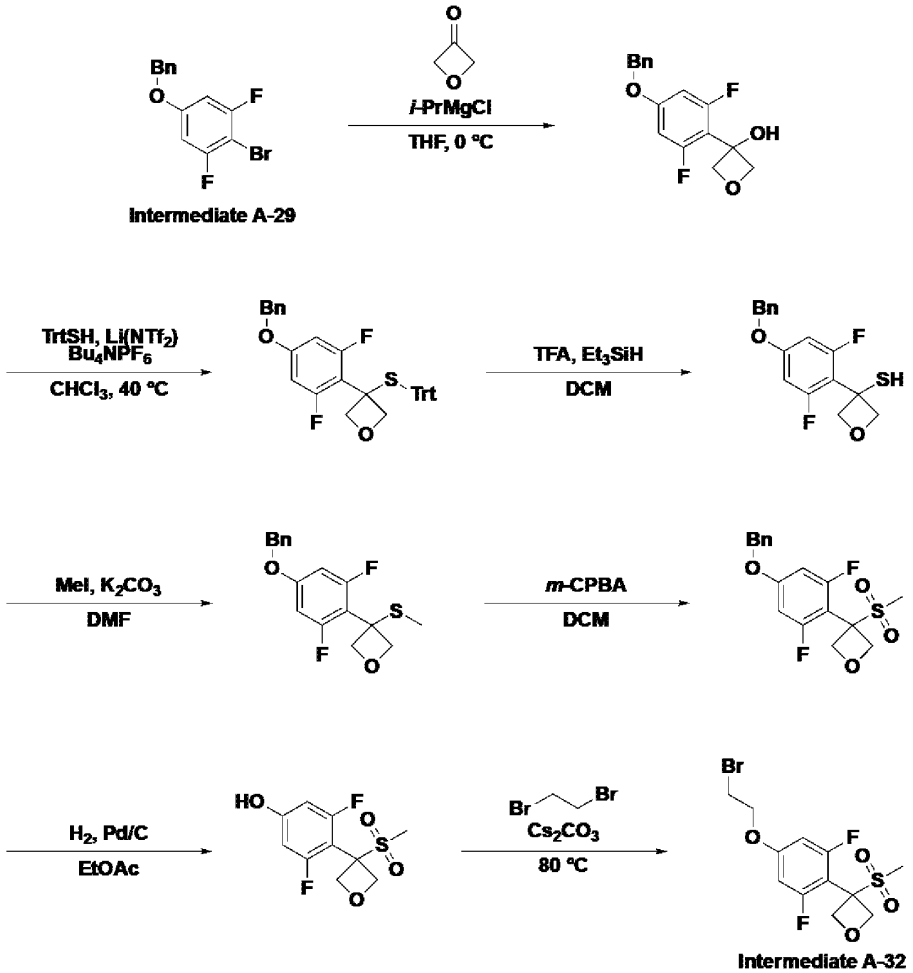
[0666] The following intermediate in Table 6 was prepared using procedures similar to those described for **Intermediate A-30**, using the appropriate starting materials.

General Procedure for Intermediate A-31

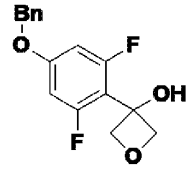
Table 6.

Intermediate #	Structure	Name	Exact Mass $[M+H]^+$
A-31		1-(2-bromoethoxy)-4-(1-methanesulfonylethyl)benzene	Calc'd 227.0 / 229.0 Found 227.1 / 229.1 $[M–CH_3O_2S]^+$

General Procedure for Intermediate A-32

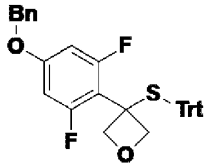


Step 1: 3-[4-(benzyloxy)-2,6-difluorophenyl]oxetan-3-ol



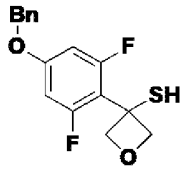
[0667] To a 0 °C solution of 5-(benzyloxy)-2-bromo-1,3-difluorobenzene (**Intermediate A-29**, 14.0 g, 46.8 mmol) in THF (150 mL) was added 2.0 M *i*-PrMgCl in THF (25.7 mL, 51.4 mmol). After stirring at 0 °C for 30 min, oxetan-3-one (4.05 g, 56.2 mmol) was added. The mixture was stirred at 0 °C for another 30 min, and then quenched with H_2O (200 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 80 g cartridge, 1:10 EtOAc:petroleum ether) to give 3-[4-(benzyloxy)-2,6-difluorophenyl]oxetan-3-ol. MS = 315.2 $[M+Na]^+$.

Step 2: 3-[4-(benzyloxy)-2,6-difluorophenyl]-3-[(triphenylmethyl)sulfanyl]oxetane



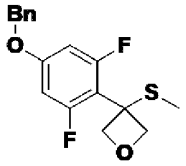
[0668] To a solution of 3-[4-(benzyloxy)-2,6-difluorophenyl]oxetan-3-ol (20.0 g, 68.4 mmol) and triphenylmethanethiol (75.7 g, 274 mmol) in $CHCl_3$ (200 mL) was added [bis(trifluoromethylsulfonyl)amino]lithium (2.16 g, 7.53 mmol) and tetrabutylammonium hexafluorophosphate (1.46 g, 3.76 mmol). The mixture was stirred at 40 °C for 2 h. After cooling to room temperature, the reaction mixture was quenched with H_2O (300 mL) and extracted with DCM (3 x 150 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 330 g cartridge, 0–40% EtOAc:petroleum ether) to give 3-[4-(benzyloxy)-2,6-difluorophenyl]-3-[(triphenylmethyl)sulfanyl]oxetane.

Step 3: 3-[4-(benzyloxy)-2,6-difluorophenyl]oxetane-3-thiol



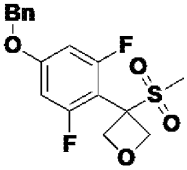
[0669] To a solution of 3-[4-(benzyloxy)-2,6-difluorophenyl]-3-[(triphenylmethyl)sulfanyl]oxetane (400 mg, 0.726 mmol) in DCM (2 mL) was added TFA (4 mL) and Et_3SiH (290 µL, 1.82 mmol). The mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with H_2O (10 mL) and extracted with DCM (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–10% EtOAc:petroleum ether) to give 3-[4-(benzyloxy)-2,6-difluorophenyl]oxetane-3-thiol. MS = 307.1 $[M–H]^-$.

Step 4: 3-[4-(benzyloxy)-2,6-difluorophenyl]-3-(methylsulfonyl)oxetane



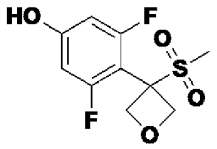
[0670] To a solution of 3-[4-(benzyloxy)-2,6-difluorophenyl]oxetane-3-thiol (2.50 g, 8.11 mmol) in DMF (25 mL) was added K_2CO_3 (1.68 g, 12.2 mmol) and MeI (2.52 mL, 40.5 mmol). The mixture was stirred at room temperature for 1 h. After cooling to 0 °C, the reaction mixture was quenched with H_2O (50 mL) and extracted with DCM (3 x 30 mL). The combined organic layers were washed with brine (3 x 30 mL) dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 80 g cartridge, 0–15% EtOAc:petroleum ether) to give 3-[4-(benzyloxy)-2,6-difluorophenyl]-3-(methylsulfonyl)oxetane. MS = 321.0 $[M–H]^-$.

Step 5: 3-[4-(benzyloxy)-2,6-difluorophenyl]-3-methanesulfonyloxetane



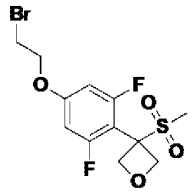
[0671] To a solution of 3-[4-(benzyloxy)-2,6-difluorophenyl]-3-(methylsulfonyl)oxetane (2.00 g, 6.20 mmol) in DCM (30 mL) was added *m*-CPBA (3.78 g, 85% purity, 18.6 mmol). The reaction mixture was diluted with H_2O (50 mL) and extracted with DCM (3 x 20 mL). The combined organic layers were washed with saturated aqueous Na_2SO_3 (2 x 20 mL) dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was triturated with EtOAc and then dried in vacuo to give 3-[4-(benzyloxy)-2,6-difluorophenyl]-3-methanesulfonyloxetane, which was used in the subsequent step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.46–7.35 (m, 5H), 6.95–6.92 (m, 2H), 5.16–5.10 (m, 6H), 3.13 (s, 3H).

Step 6: 3,5-difluoro-4-(3-methanesulfonyloxetan-3-yl)phenol



[0672] To a solution of 3-[4-(benzyloxy)-2,6-difluorophenyl]-3-methanesulfonyloxetane (600 mg, 1.69 mmol) in EtOAc (20 mL) under Argon atmosphere was added Pd/C (1.00 g, 10 wt%, 0.943 mmol). The mixture was stirred at room temperature for 3 h under an atmosphere of H_2 (15 psi). The reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo to give 3,5-difluoro-4-(3-methanesulfonyloxetan-3-yl)phenol, which was used in the subsequent step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6, 9/10 H): δ 6.54–6.51 (m, 2H), 5.13–5.08 (m, 4H), 3.09 (s, 3H).

Step 7: 3-[4-(2-bromoethoxy)-2,6-difluorophenyl]-3-methanesulfonyloxetane



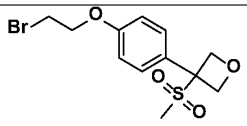
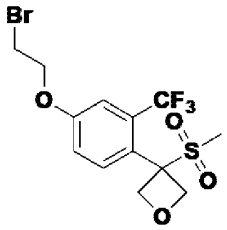
[0673] To a solution of 3,5-difluoro-4-(3-methanesulfonyloxetan-3-yl)phenol (200 mg, 0.757 mmol) in 1,2-dibromoethane (2.00 mL, 26.5 mmol) was added Cs_2CO_3 (493 mg, 1.51 mmol). The mixture was stirred at 80 °C for 3 h. After cooling to 0 °C, the reaction mixture was quenched with H_2O (10 mL) and extracted with DCM (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica

gel chromatography (Biotage 4 g cartridge, 0–40% EtOAc:petroleum ether) to give 3-[4-(2-bromoethoxy)-2,6-difluorophenyl]-3-methanesulfonyloxetane (**Intermediate A-32**). MS = 388.0 / 390.0 $[M+NH_4]^+$.

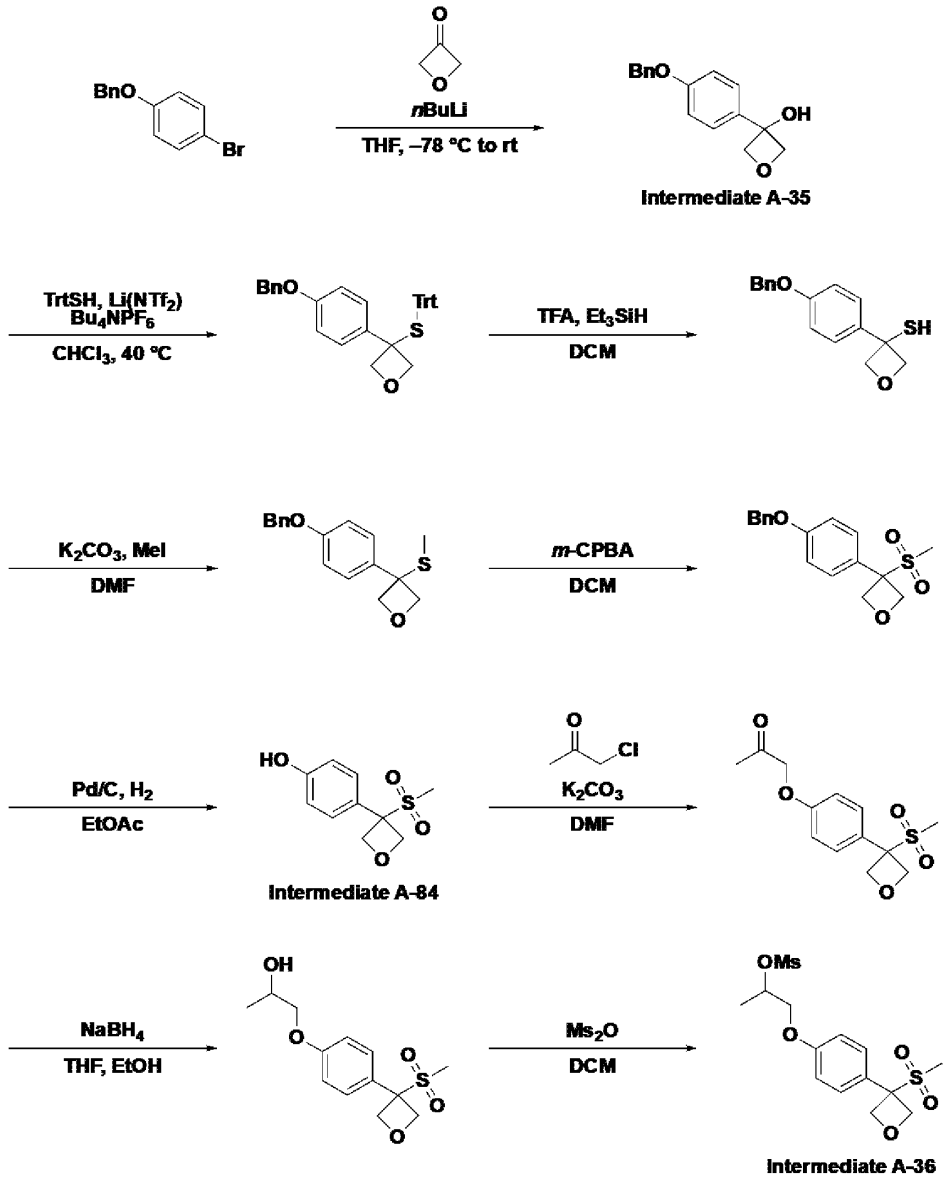
[0674] The following intermediates in Table 7 were prepared using procedures similar to those described for **Intermediate A-32**, using the appropriate starting materials.

General Procedure for Intermediates A-33 & A-34

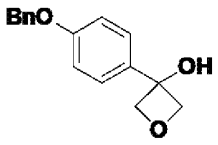
Table 7.

Intermediate #	Structure	Name	Exact Mass $[M+H]^+$
A-33		3-[4-(2-bromoethoxy)phenyl]-3-methanesulfonyloxetane	Calc'd 352.0 / 354.0 Found 352.1 / 354.0 $[M+NH_4]^+$
A-34		3-[4-(2-bromoethoxy)-2-(trifluoromethyl)phenyl]-3-methanesulfonyloxetane	Calc'd 420.0 / 422.0 Found 420.0 / 422.0 $[M+NH_4]^+$

General Procedure for Intermediates A-35, A-36, & A-84

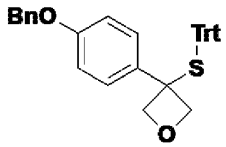


Step 1: 3-[4-(benzyloxy)phenyl]oxetane-3-ol



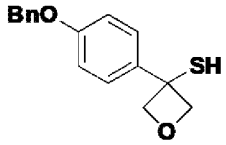
[0675] To a –78°C solution of 1-(benzyloxy)-4-bromobenzene (3.00 g, 11.4 mmol) in THF (20 mL) was added 2.5 M *n*-BuLi in THF (7.30 mL, 18.3 mmol). After stirring for 1 h at –78 °C, oxetan-3-one (986 mg, 13.7 mmol) was added. The mixture was warmed to room temperature and stirred for 3 h. The reaction mixture cooled to 0 °C, quenched with H_2O (30 mL), and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 45 g cartridge, 0–50% EtOAc:petroleum ether) to give 3-[4-(benzyloxy)phenyl]oxetan-3-ol (**Intermediate A-35**). MS = 279.1 $[M+Na]^+$.

Step 2: 3-[4-(benzyloxy)phenyl]-3-[(triphenylmethyl)sulfanyl]oxetane



[0676] To a solution of 3-[4-(benzyloxy)phenyl]oxetan-3-ol (7.40 g, 28.9 mmol) and triphenylmethanethiol (39.9 g, 144 mmol) in $CHCl_3$ (80 mL) were added [bis(trifluoromethylsulfonyl)amino]lithium (911 mg, 3.18 mmol) and tetrabutylammonium hexafluorophosphate (615 mg, 1.59 mmol). The mixture was stirred at 40 °C for 30 min. After cooling to room temperature, the reaction mixture was quenched with H_2O (80 mL) and extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 120 g cartridge, 0–40% EtOAc:petroleum ether) to give 3-[4-(benzyloxy)phenyl]-3-[(triphenylmethyl)sulfanyl]oxetane. MS = 537.3 $[M+Na]^+$.

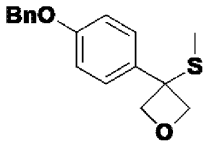
Step 3: 3-[4-(benzyloxy)phenyl]oxetane-3-thiol



[0677] To a solution of 3-[4-(benzyloxy)phenyl]-3-[(triphenylmethyl)sulfanyl]oxetane (10.0 g, 19.4 mmol) in DCM (40 mL) was added TFA (60.0 mL, 810 mmol) and Et_3SiH (7.76 mL, 48.6 mmol). The mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with H_2O (80 mL) and extracted with DCM (3 x 50 mL). The combined organic layers were washed

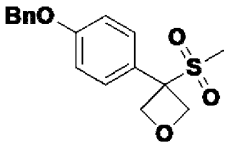
with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 3-(4-benzyloxyphenyl)oxetane-3-thiol, which was used in the subsequent step without further purification. MS = 273.1 $[M+H]^+$.

Step 4: 3-[4-(benzyloxy)phenyl]-3-(methylsulfanyl)oxetane



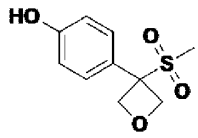
[0678] To a solution of 3-(4-benzyloxyphenyl)oxetane-3-thiol (5.00 g, 18.4 mmol) in DMF (40 mL) was added MeI (13.0 g, 91.8 mmol) and K_2CO_3 (3.81 g, 27.5 mmol). The mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with H_2O (80 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 80 g cartridge, 0–30% EtOAc:petroleum ether) to give 3-[4-(benzyloxy)phenyl]-3-(methylsulfanyl)oxetane. ^1H NMR (400 MHz, $CDCl_3$): δ 7.46–7.39 (m, 5H), 7.11 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 5.18 (d, J = 6.4 Hz, 2H), 5.08 (s, 2H), 4.90 (d, J = 6.4 Hz, 2H), 2.04 (s, 3H).

Step 5: 3-[4-(benzyloxy)phenyl]-3-methanesulfonyloxetane



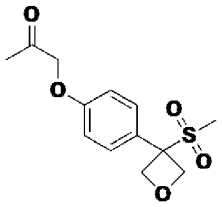
[0679] To a 0 °C solution of 3-[4-(benzyloxy)phenyl]-3-(methylsulfanyl)oxetane (3.25 g, 11.4 mmol) in DCM (40 mL) was added m-CPBA (6.91 g, 85% purity, 34.04 mmol). The mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with saturated aqueous Na_2SO_3 (20 mL), diluted with H_2O (60 mL), and extracted with DCM (3 x 40 mL). The combined organic layers were with saturated aqueous $NaHCO_3$ (3 x 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was triturated with EtOAc, the solids were collected via filtration, and the filter cake was dried in vacuo to give 3-[4-(benzyloxy)phenyl]-3-methanesulfonyloxetane. MS = 336.2 $[M+NH_4]^+$.

Step 6: 4-(3-methanesulfonyloxetan-3-yl)phenol



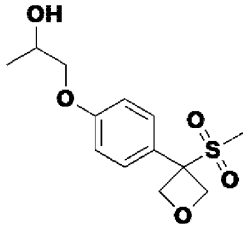
[0680] To a solution of 3-[4-(benzyloxy)phenyl]-3-methanesulfonyloxetane (1.60 g, 5.03 mmol) in EtOAc (100 mL) under N_2 atmosphere was added Pd/C (2.00 g, 10 wt%, 1.89 mmol). The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at room temperature for 10 h. The reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo give 4-(3-methanesulfonyloxetan-3-yl)phenol (**Intermediate A-84**), which was used in the subsequent step without further purification. MS = 246.1 $[M+NH_4]^+$.

Step 7: 1-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]propan-2-one



[0681] To a solution of 4-(3-methylsulfonyloxetan-3-yl)phenol (500 mg, 2.19 mmol) in DMF (5 mL) was added K_2CO_3 (605 mg, 4.38 mmol) and 1-chloropropan-2-one (304 mg, 3.29 mmol). The mixture was stirred at room temperature for 1 h. The reaction mixture was cooled to 0 °C and quenched with H_2O (15 mL), and then extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give 1-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]propan-2-one, which was used in the subsequent step without further purification. MS = 302.2 $[M+ NH_4]^+$.

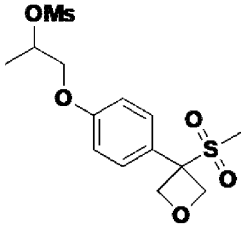
Step 8: 1-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]propan-2-ol



[0682] To a solution of 1-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]propan-2-one (600 mg, 2.11 mmol) in THF (15 mL) and EtOH (2 mL) was added $NaBH_4$ (120 mg, 3.17 mmol). The

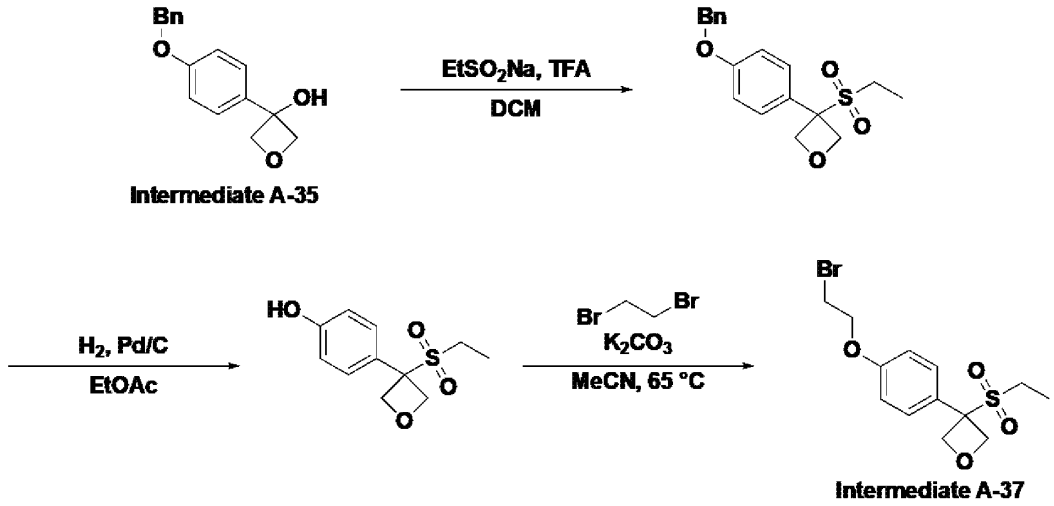
mixture was stirred at room temperature for 30 min. The reaction mixture was cooled to 0 °C, quenched with H_2O (15 mL), and the solution was adjusted to pH = 6–7 with the dropwise addition of 4.0 M aqueous HCl. The mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give 1-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]propan-2-ol, which was used in the subsequent step without further purification. MS = 304.1 $[M+NH_4]^+$.

Step 9: 1-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]propan-2-yl methanesulfonate

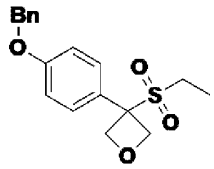


[0683] To a solution of 1-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]propan-2-ol (570 mg, 1.99 mmol) in DCM (15 mL) was added TEA (0.831 mL, 5.97 mmol) and methanesulfonic anhydride (694 mg, 3.98 mmol). The mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with H_2O (15 mL), and the solution was adjusted to pH = 6 with the dropwise addition of 4.0 M aqueous HCl. The mixture was extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give 1-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]propan-2-yl methanesulfonate, which was used in the subsequent step without further purification (**Intermediate A-36**). MS = 382.1 $[M+NH_4]^+$.

General Procedure for Intermediate A-37

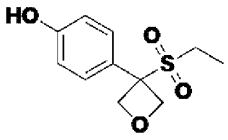


Step 1: 3-[4-(benzyloxy)phenyl]-3-(ethanesulfonyl)oxetane



[0684] To a 0 °C solution of 3-[4-(benzyloxy)phenyl]oxetan-3-ol (**Intermediate A-35**, 400 mg, 1.56 mmol) in DCM (5 mL) was added sodium ethanesulfinate (906 mg, 7.80 mmol) and TFA (2.31 mL, 31.2 mmol). The mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with H_2O (30 mL). The resulting precipitate was collected by filtration and dried in vacuo to give 3-[4-(benzyloxy)phenyl]-3-(ethanesulfonyl)oxetane. MS = 350.1 $[M+NH_4]^+$.

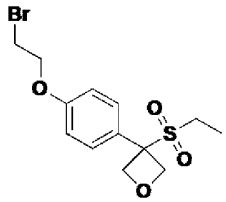
Step 2: 4-[3-(ethanesulfonyl)oxetan-3-yl]phenol



[0685] To a solution of 3-[4-(benzyloxy)phenyl]-3-(ethanesulfonyl)oxetane (400 mg, 1.20 mmol) in EtOAc (20 mL) under N_2 atmosphere was added Pd/C (1.00 g, 10 wt%, 0.943 mmol). The suspension was degassed under vacuum and purged with H_2 (3x). The mixture was stirred under H_2 (15 psi) at room temperature for 3 h. The reaction mixture was filtered through Celite and the filtrate

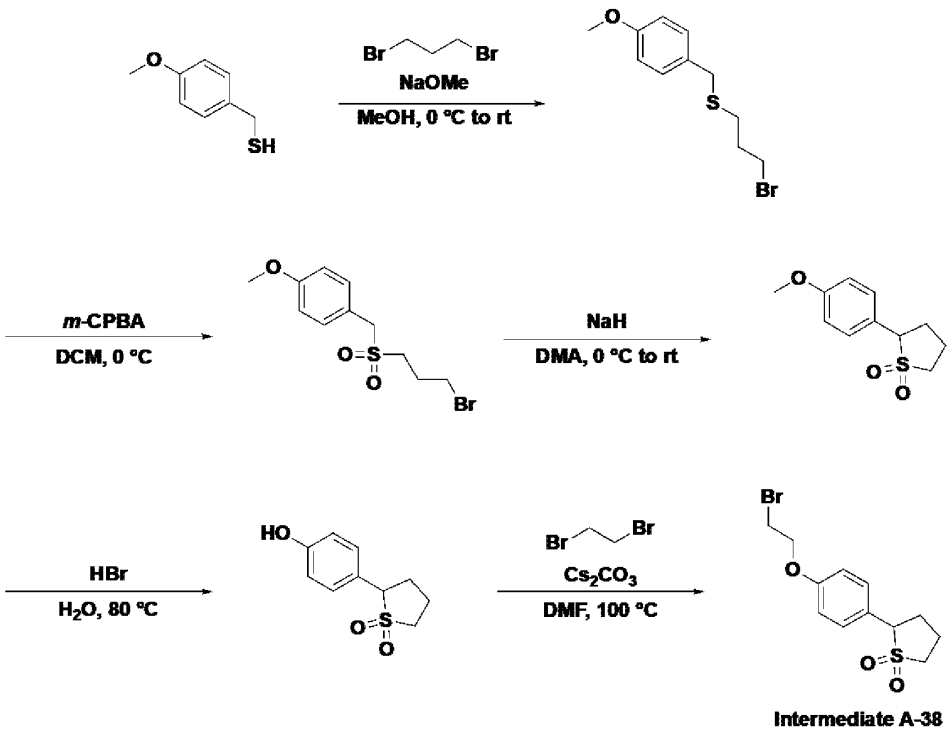
was concentrated in vacuo to give 4-[3-(ethanesulfonyl)oxetan-3-yl]phenol, which was used in the subsequent step without further purification.

Step 3: 3-[4-(2-bromoethoxy)phenyl]-3-(ethanesulfonyl)oxetane

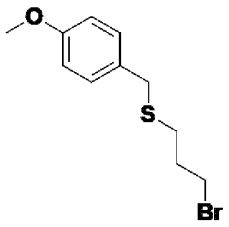


[0686] To a solution of 4-[3-(ethanesulfonyl)oxetan-3-yl]phenol (150 mg, 0.619 mmol) in MeCN (4 mL) were added K_2CO_3 (428 mg, 3.10 mmol) and 1,2-dibromoethane (1.87 mL, 24.8 mmol). The mixture was stirred at 65 °C for 10 h. After cooling to room temperature, the reaction mixture was filtered, washed with MeCN (20 mL), and the filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 4 g cartridge, 0–45% EtOAc:petroleum ether) to give 3-[4-(2-bromoethoxy)phenyl]-3-(ethanesulfonyl)oxetane (**Intermediate A-37**). MS = 366.0 / 368.0 $[M+NH_4]^+$.

General Procedure for Intermediate A-38

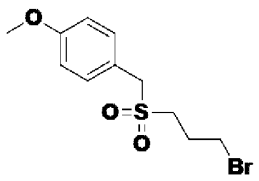


Step 1: 1-{[(3-bromopropyl)sulfanyl]methyl}-4-methoxybenzene



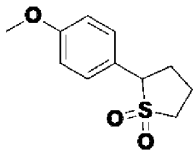
[0687] To a solution of (4-methoxyphenyl)methanethiol (9.01 mL, 64.8 mmol) and 1,3-dibromopropane (33.1 mL, 324 mmol) in MeOH (50 mL) was added NaOMe (5.25 g, 97.3 mmol). The reaction mixture stirred at room temperature for 16 h. After cooling to 0 °C, the reaction mixture was quenched with H_2O (200 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over (Na_2SO_4), filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 120 g cartridge, 0–10% EtOAc:petroleum ether) to give 1-{[(3-bromopropyl)sulfanyl]methyl}-4-methoxybenzene.

Step 2: 1-[(3-bromopropanesulfonyl)methyl]-4-methoxybenzene



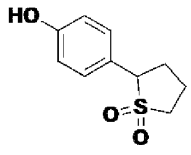
[0688] To a 0 °C solution of 1-{[(3-bromopropyl)sulfanyl]methyl}-4-methoxybenzene (5.00 g, 18.2 mmol) in DCM (100 mL) was added m-CPBA (9.22 g, 85% purity, 45.4 mmol). The mixture was stirred at 0 °C for 2 h and was then quenched with saturated Na_2SO_3 (50 mL). The organic layer was separated, washed with saturated $NaHCO_3$ (2 x 100 mL), brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 120 g cartridge, 0–50% EtOAc:petroleum ether) to give 1-[(3-bromopropanesulfonyl)methyl]-4-methoxybenzene.

Step 3: 2-(4-methoxyphenyl)-1λ⁶-thiolane-1,1-dione



[0689] To a 0 °C solution of 1-[(3-bromopropanesulfonyl)methyl]-4-methoxybenzene (3.00 g, 9.77 mmol) in DMA (30 mL) was added NaH (898 mg, 60 wt% in mineral oil, 22.5 mmol). The mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was quenched with ice water (20 mL), diluted with H_2O (10 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 25 g cartridge, 0–100% EtOAc:petroleum ether) to give 2-(4-methoxyphenyl)-1λ⁶-thiolane-1,1-dione. MS = 227.2 $[M+H]^+$.

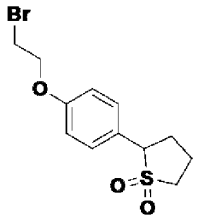
Step 4: 2-(4-hydroxyphenyl)-1λ⁶-thiolane-1,1-dione



[0690] A solution of 2-(4-methoxyphenyl)-1λ⁶-thiolane-1,1-dione (1.00 g, 4.42 mmol) in HBr in H_2O (10 mL, 45 wt%) was stirred at 80 °C for 16 h. After cooling to room temperature, the reaction

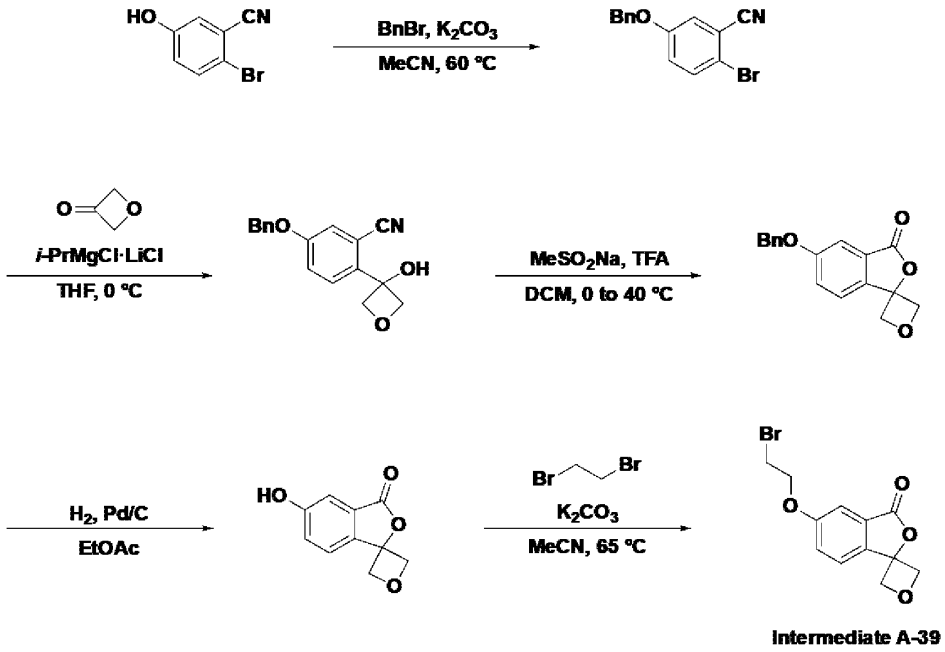
mixture was concentrated in vacuo. The residue was diluted with H_2O (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 25 g cartridge, 0–100% EtOAc:petroleum ether) to give 2-(4-hydroxyphenyl)-1λ⁶-thiolane-1,1-dione. MS = 213.1 $[M+H]^+$.

Step 5: 2-[4-(2-bromoethoxy)phenyl]-1λ⁶-thiolane-1,1-dione

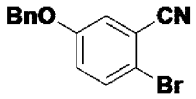


[0691] To a mixture of 2-(4-hydroxyphenyl)-1λ⁶-thiolane-1,1-dione (660 mg, 3.11 mmol) and 1,2-dibromoethane (2.35 mL, 31.1 mmol) in DMF (5 mL) was added Cs_2CO_3 (3.04 g, 9.33 mmol). The reaction mixture was stirred at 100 °C for 16 h. After cooling to room temperature, the mixture was diluted with H_2O (30 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 25 g cartridge, 0–100% EtOAc:petroleum ether) to give 2-(4-hydroxyphenyl)-1λ⁶-thiolane-1,1-dione (**Intermediate A-38**). MS = 319.0 / 321.0 $[M+H]^+$.

General Procedure for Intermediate A-39

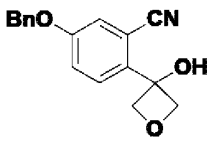


Step 1: 5-(benzyloxy)-2-bromobenzonitrile



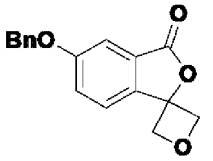
[0692] To a solution of 2-bromo-5-hydroxybenzonitrile (15.0 g, 75.8 mmol) in MeCN (160 mL) were added benzyl bromide (10.8 mL, 90.9 mmol) and K_2CO_3 (15.7 g, 114 mmol). The mixture was stirred at 60 °C for 15 h. After cooling to room temperature, the reaction mixture was filtered to remove solids. The filtrate was diluted with water (60 mL) and extracted with EtOAc (3 x 80 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was triturated with petroleum ether and dried in vacuo to give 5-(benzyloxy)-2-bromobenzonitrile, which was used in the subsequent step without further purification.

Step 2: 5-(benzyloxy)-2-(3-hydroxyoxetan-3-yl)benzonitrile



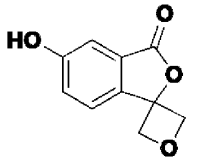
[0693] To a 0 °C solution of 5-(benzyloxy)-2-bromobenzonitrile (10.0 g, 34.7 mmol) in THF (120 mL) was slowly added 1.3 M i-PrMgCl.LiCl in THF (34.71 mL, 45.1 mmol). After stirring for 10 min, oxetan-3-one (3.50 g, 48.59 mmol) was added to the mixture, and stirring was continued for another 2 h. The reaction mixture was quenched with saturated aqueous NH4Cl (80 mL) and stirred for 30 min, and then was extracted with EtOAc (3 x 80 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 120 g cartridge, 0–20% EtOAc:petroleum ether) to give 5-(benzyloxy)-2-(3-hydroxyoxetan-3-yl)benzonitrile. MS = 282.2 $[M+H]^+$.

Step 3: 5-(benzyloxy)-3H-spiro[2-benzofuran-1,3'-oxetan]-3-one



[0694] To a 0 °C solution of 5-(benzyloxy)-2-(3-hydroxyoxetan-3-yl)benzonitrile (1.50 g, 5.33 mmol) in DCM (20 mL) was added sodium methanesulfinate (2.72 g, 26.7 mmol) followed by the dropwise addition of TFA (3.95 mL, 53.3 mmol). The mixture was stirred at 40 °C for 15 h. After cooling to room temperature, the reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 0–25% EtOAc:petroleum ether) to give 5-(benzyloxy)-3H-spiro[2-benzofuran-1,3'-oxetan]-3-one. MS = 283.2 $[M+H]^+$.

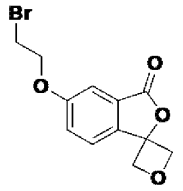
Step 4: 5-hydroxy-3H-spiro[2-benzofuran-1,3'-oxetan]-3-one



[0695] To a solution of 5-(benzyloxy)-3H-spiro[2-benzofuran-1,3'-oxetan]-3-one (900 mg, 3.19 mmol) in MeOH (25 mL) was added Pd/C (200 mg, 10 wt%, 0.189 mmol). The mixture was stirred at room temperature for 15 h under H_2 (15 psi). The reaction mixture was filtered and concentrated

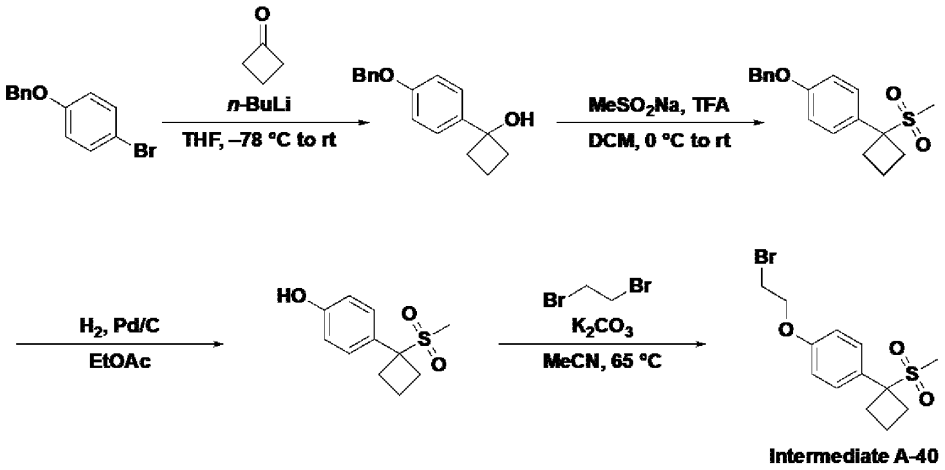
in vacuo to give 5-(benzyloxy)-3H-spiro[2-benzofuran-1,3'-oxetan]-3-one, which was used in the subsequent step without further purification. MS = 193.2 $[M+H]^+$.

Step 5: 5-(2-bromoethoxy)-3H-spiro[2-benzofuran-1,3'-oxetan]-3-one

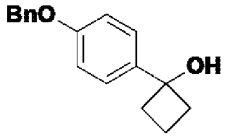


[0696] To a solution of 5-(benzyloxy)-3H-spiro[2-benzofuran-1,3'-oxetan]-3-one (420 mg, 2.19 mmol) in MeCN (5 mL) were added K_2CO_3 (1.51 g, 10.9 mmol) and 1,2-dibromoethane (6.60 mL, 87.4 mmol). The mixture was stirred at 65 °C for 15 h. After cooling to room temperature, the reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–33% EtOAc:petroleum ether) to give 5-(2-bromoethoxy)-3H-spiro[2-benzofuran-1,3'-oxetan]-3-one (**Intermediate A-39**). MS = 299.0 / 301.1 $[M+H]^+$.

General Procedure for Intermediate A-40

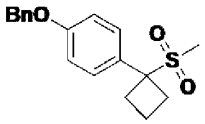


Step 1: 1-[4-(benzyloxy)phenyl]cyclobutan-1-ol



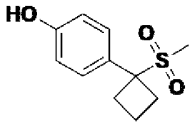
[0697] To a –78 °C solution of 1-(benzyloxy)-4-bromobenzene (5.00 g, 19.0 mmol) in THF (50 mL) was added 2.5 M *n*-BuLi in THF (12.16 mL, 30.4 mmol). After stirring at –78 °C for 30 min, cyclobutanone (1.70 mL, 22.8 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was cooled to 0 °C, quenched with saturated aqueous NH_4Cl (50 mL), and then extracted with EtOAc (3 x 70 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 40 g cartridge, 0–15% EtOAc:petroleum ether) to give 1-[4-(benzyloxy)phenyl]cyclobutan-1-ol. ^{1}H NMR (400 MHz, DMSO-d_6, 17/18 H): δ 7.46–7.38 (m, 7H), 6.99 (d, J = 8.8 Hz, 2H), 5.09 (s, 2H), 2.57–2.54 (m, 2H), 2.40–2.35 (m, 2H), 2.00–1.98 (m, 1H), 1.69–1.64 (m, 1H).

Step 2: 1-(benzyloxy)-4-(1-methanesulfonylcyclobutyl)benzene



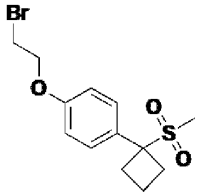
[0698] To a 0 °C solution of 1-[4-(benzyloxy)phenyl]cyclobutan-1-ol (3.80 g, 14.9 mmol) and sodium methanesulfinate (10.7 g, 105 mmol) in DCM (40 mL) was added TFA (22.1 mL, 299 mmol). The mixture was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was cooled to 0 °C and quenched with H_2O (50 mL). The resulting biphasic mixture was adjusted to pH = 6–7 with saturated aqueous Na_2CO_3 and then extracted with DCM (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was triturated with 1:1 petroleum ether:EtOAc. The mixture was filtered, the filter cake was washed with EtOAc, and dried in vacuo to give 1-(benzyloxy)-4-(1-methanesulfonylcyclobutyl)benzene, which was used in the subsequent step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.46–7.34 (m, 7H), 7.04 (d, J = 8.8 Hz, 2H), 5.12 (s, 2H), 2.94–2.91 (m, 2H), 2.61 –2.55 (m, 5H), 2.09–2.07 (m, 1H), 1.89–1.86 (m, 1H).

Step 3: 4-(1-methanesulfonylcyclobutyl)phenol



[0699] To a solution of 1-(benzyloxy)-4-(1-methanesulfonylcyclobutyl)benzene (2.60 g, 8.22 mmol) in EtOAc (100 mL) under a N_2 environment was added Pd/C (2.00 g, 10 wt%, 1.89 mmol). The suspension was degassed under vacuum and purged with H_2 (3x). The mixture was stirred under H_2 (15 psi) at room temperature for 5 h. The reaction mixture was filtered through Celite, the filter cake was washed with EtOAc, and the filtrate was concentrated in vacuo to give 1-(benzyloxy)-4-(1-methanesulfonylcyclobutyl)benzene, which was used in the subsequent step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.64 (s, 1H), 7.20 (d, J = 6.8 Hz, 2H), 6.77 (d, J = 6.8 Hz, 2H), 2.91–2.87 (m, 2H), 2.58 (s, 3H), 2.56–2.52 (m, 2H), 2.08–2.05 (m, 1H), 1.88–1.84 (s, 1H).

Step 4: 1-(2-bromoethoxy)-4-(1-methanesulfonylcyclobutyl)benzene



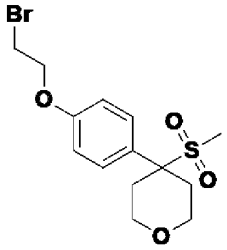
[0700] A mixture of 1-(benzyloxy)-4-(1-methanesulfonylcyclobutyl)benzene (500 mg, 2.21 mmol), 1,2-dibromoethane (6.67 mL, 88.4 mmol) and K_2CO_3 (1.53 g, 11.1 mmol) in MeCN (10 mL) was stirred at 65 °C for 16 h. After cooling to room temperature, the reaction mixture was filtered and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–30% EtOAc:petroleum ether) to give 1-(2-bromoethoxy)-4-(1-methanesulfonylcyclobutyl)benzene (**Intermediate A-40**). MS = 350.1 / 352.1 $[M+NH_4]^+$.

[0701] The following intermediate in Table 8 was prepared according to procedures similar those described for **Intermediate A-40** using the appropriate starting materials.

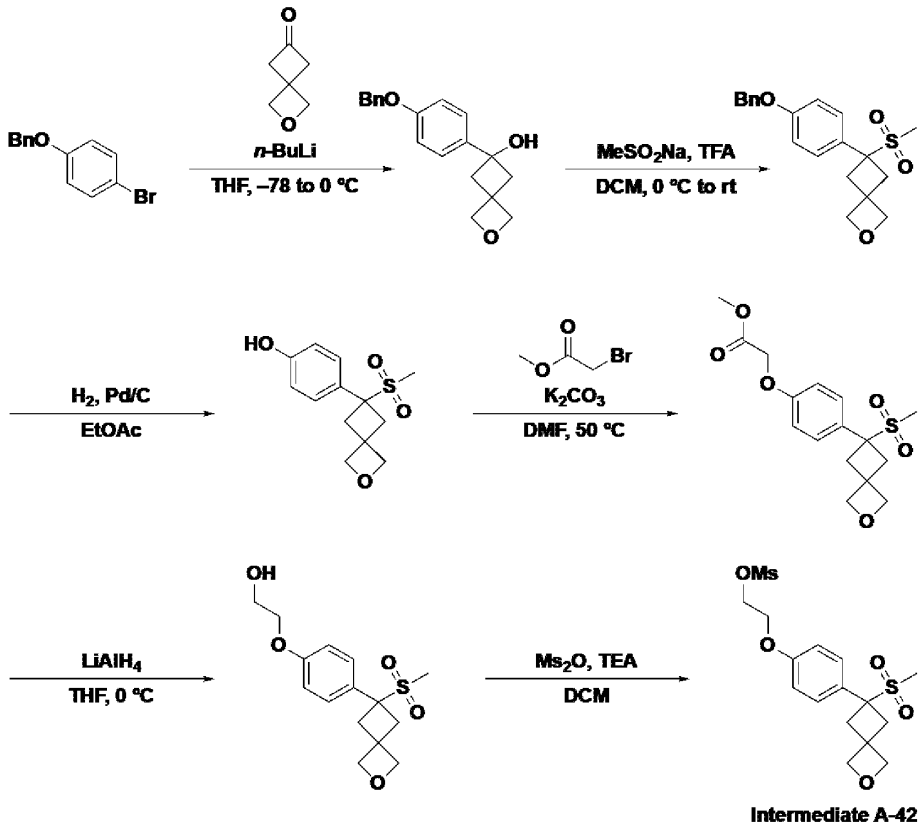
General Procedure for Intermediate A-41

Table 8.

Intermediate #	Structure	Name	Exact Mass $[M+H]^+$

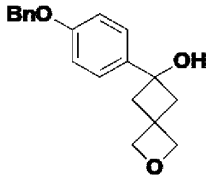
A-41		4-[4-(2-bromoethoxy)phenyl]-4-methanesulfonyloxane	Calc'd 380.1 / 382.1 Found 380.1 / 382.1 $[M+NH_4]^+$

General Procedure for Intermediate A-42



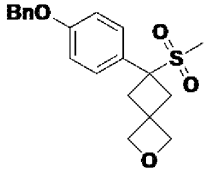
Intermediate A-42

Step 1: 6-[4-(benzyloxy)phenyl]-2-oxaspiro[3.3]heptan-6-ol



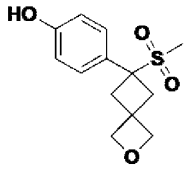
[0702] To a –78 °C solution of 1-(benzyloxy)-4-bromobenzene (2.68 g, 10.2 mmol) in THF (10 mL) was added 2.5 M *n*-BuLi in THF (4.74 mL, 11.9 mmol). After stirring for 20 min, a solution of 2-oxaspiro[3.3]heptan-6-one (950 mg, 8.47 mmol) in THF (3 mL) was added. The mixture was stirred at –78°C for 30 min. The reaction mixture was warmed to 0 °C, quenched with saturated aqueous NH_4Cl (15 mL), and then extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 6-[4-(benzyloxy)phenyl]-2-oxaspiro[3.3]heptan-6-ol. MS = 279.1 $[M–OH]^+$.

Step 2: 6-[4-(benzyloxy)phenyl]-6-methanesulfonyl-2-oxaspiro[3.3]heptane



[0703] To a solution of 6-[4-(benzyloxy)phenyl]-2-oxaspiro[3.3]heptan-6-ol (2.00 g, 6.75 mmol) in DCM (30 mL) were added sodium methanesulfinate (3.44 g, 33.7 mmol), and TFA (9.99 mL, 135 mmol). The mixture was stirred at room temperature for 3 h. The reaction mixture was cooled to 0 °C, quenched with H_2O (50 mL), and then extracted with DCM (2 x 15 mL). The combined organic layers were washed with brine (30 mL x 2), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 0–50% EtOAc:petroleum ether) to give 6-[4-(benzyloxy)phenyl]-6-methanesulfonyl-2-oxaspiro[3.3]heptane. MS = 359.1 $[M+H]^+$.

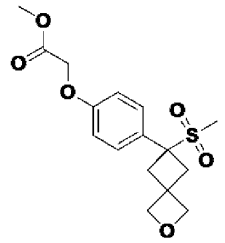
Step 3: 4-{6-methanesulfonyl-2-oxaspiro[3.3]heptan-6-yl}phenol



[0704] To a solution of 6-[4-(benzyloxy)phenyl]-6-methanesulfonyl-2-oxaspiro[3.3]heptane (400 mg, 1.12 mmol) in EtOAc (10 mL) under N_2 atmosphere was added Pd/C (200 mg, 10 wt%, 1.89 mmol). The suspension was degassed under vacuum and purged with H_2 (3x). The mixture was stirred under H_2 (15 psi) at room temperature for 3 h. The mixture was filtered through Celite and

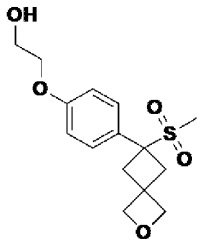
the filtrate was concentrated in vacuo to give 4-{6-methanesulfonyl-2-oxaspiro[3.3]heptan-6-yl}phenol, which was used in the subsequent step without further purification.

Step 4: methyl 2-(4-{6-methanesulfonyl-2-oxaspiro[3.3]heptan-6-yl}phenoxy)acetate



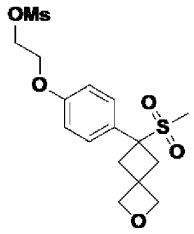
[0705] A mixture of 4-{6-methanesulfonyl-2-oxaspiro[3.3]heptan-6-yl}phenol (240 mg, 0.894 mmol), methyl 2-bromoacetate (0.169 mL, 1.79 mmol), and K_2CO_3 (309 mg, 2.24 mmol) in DMF (5 mL) was degassed and purged with N_2 (3x). The mixture was stirred at 50 °C for 3 h under N_2 atmosphere. The reaction mixture was cooled to 0 °C, quenched with H_2O (15 mL), and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give methyl 2-(4-{6-methanesulfonyl-2-oxaspiro[3.3]heptan-6-yl}phenoxy)acetate. MS = 341.1 $[M+H]^+$.

Step 5: 2-(4-{6-methanesulfonyl-2-oxaspiro[3.3]heptan-6-yl}phenoxy)ethan-1-ol



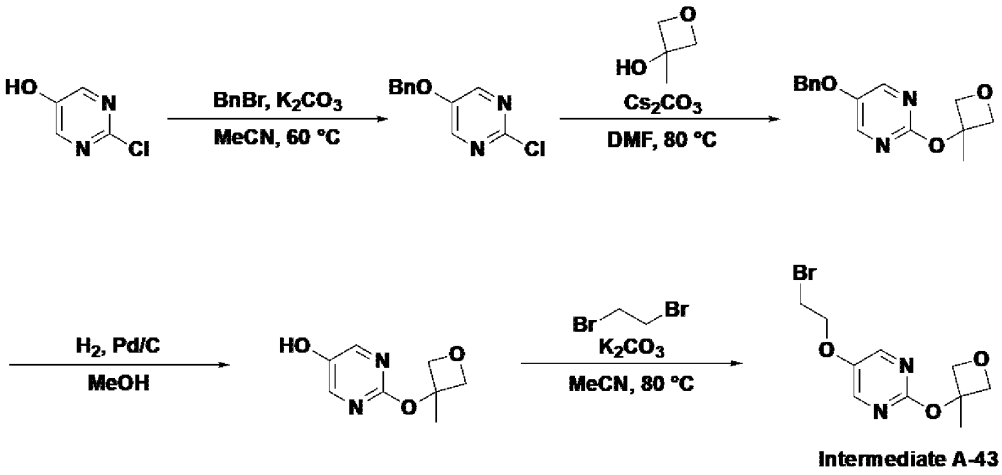
[0706] To a 0 °C solution of methyl 2-(4-{6-methanesulfonyl-2-oxaspiro[3.3]heptan-6-yl}phenoxy)acetate (300 mg, 0.881 mmol) in THF (10 mL) under a N_2 environment was added $LiAlH_4$ (66.9 mg, 1.76 mmol). The mixture was stirred at 0 °C for 30 min, and then was quenched with H_2O (15 mL). The resulting biphasic mixture was adjusted to pH = 6–7 with 2.0 M aqueous HCl solution, and then was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give 2-(4-{6-methanesulfonyl-2-oxaspiro[3.3]heptan-6-yl}phenoxy)ethan-1-ol, which was used in the subsequent step without further purification. MS = 313.1 $[M+H]^+$.

Step 6: 2-(4-{6-methanesulfonyl-2-oxaspiro[3.3]heptan-6-yl}phenoxy)ethyl methanesulfonate



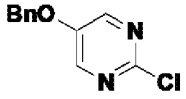
[0707] To a solution of 2-(4-{6-methanesulfonyl-2-oxaspiro[3.3]heptan-6-yl}phenoxy)ethan-1-ol (280 mg, 0.896 mmol) in DCM (5 mL) was added TEA (0.250 mL, 1.79 mmol) and methanesulfonic anhydride (234 mg, 1.34 mmol). The mixture was stirred at room temperature for 1 h, and then was quenched with H_2O (10 mL). The resulting biphasic mixture was adjusted to pH = 6–7 with 2.0 M aqueous HCl solution, and then was extracted with DCM (2 x 10 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give 2-(4-{6-methanesulfonyl-2-oxaspiro[3.3]heptan-6-yl}phenoxy)ethyl methanesulfonate (**Intermediate A-42**), which was used in the subsequent step without further purification. MS = 391.1 $[M+H]^+$.

General Procedure for Intermediate A-43



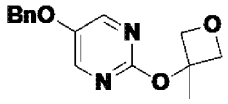
Intermediate A-43

Step 1: 5-(benzyloxy)-2-chloropyrimidine



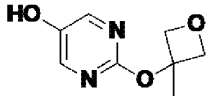
[0708] To a solution of 2-chloropyrimidin-5-ol (5.00 g, 38.3 mmol) and benzyl bromide (5.46 mL, 46.0 mmol) in MeCN (50 mL) was added K_2CO_3 (7.94 g, 57.5 mmol). The mixture was stirred at 60 °C for 2 h. After cooling to room temperature, the mixture was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 40 g cartridge, 0–15% EtOAc:petroleum ether) to give 5-(benzyloxy)-2-chloropyrimidine. MS = 221.1 $[M+H]^+$.

Step 2: 5-(benzyloxy)-2-[(3-methyloxetan-3-yl)oxy]pyrimidine



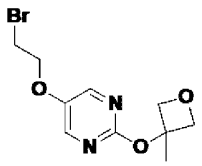
[0709] To a solution of 3-methyloxetan-3-ol (1.20 g, 13.6 mmol) and 5-benzyloxy-2-chloro-pyrimidine (1.00 g, 4.53 mmol) in DMF (20 mL) was added Cs_2CO_3 (4.43 g, 13.6 mmol). The mixture was stirred at room temperature for 6 h. Solids were removed by filtration, and the filtrate was concentrated under reduced pressure. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 0–15% EtOAc:petroleum ether) to give 5-(benzyloxy)-2-[(3-methyloxetan-3-yl)oxy]pyrimidine. MS = 273.1 $[M+H]^+$.

Step 3: 2-[(3-methyloxetan-3-yl)oxy]pyrimidin-5-ol



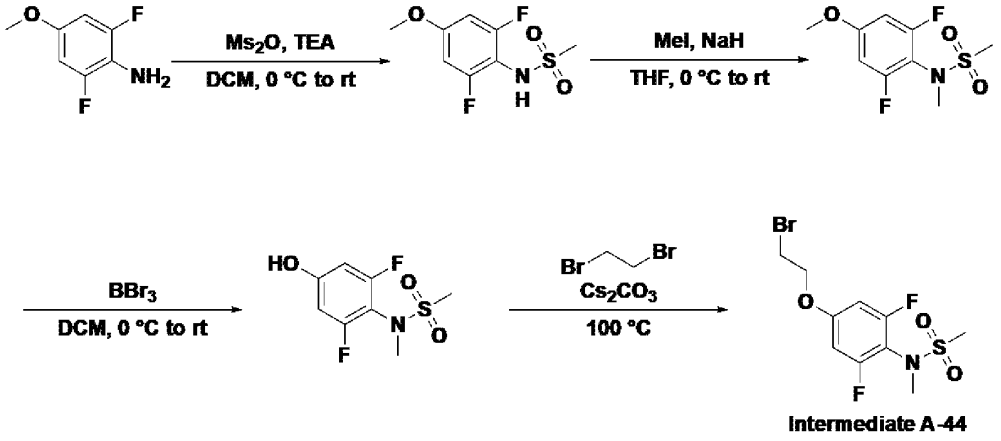
[0710] To a suspension of Pd/C (150 mg, 10 wt%, 0.14 mmol) in MeOH (15 mL) was added 5-(benzyloxy)-2-[(3-methyloxetan-3-yl)oxy]pyrimidine (600 mg, 2.20 mmol) under an atmosphere of N_2. The suspension was degassed and purged with H_2 (3x). The mixture was stirred at room temperature under H_2 (15 psi) for 3 h. The mixture was filtered through a pad of Celite, and the filter cake was washed with MeOH. The filtrate was concentrated in vacuo to give 2-[(3-methyloxetan-3-yl)oxy]pyrimidin-5-ol. MS = 183.1 $[M+H]^+$.

Step 4: 5-(2-bromoethoxy)-2-[(3-methyloxetan-3-yl)oxy]pyrimidine

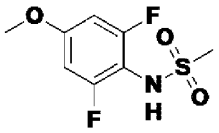


[0711] To a solution of 2-[(3-methyloxetan-3-yl)oxy]pyrimidin-5-ol (370 mg, 2.03 mmol) and 1,2-dibromoethane (6.13 mL, 81.2 mmol) in MeCN (8 mL) was added K_2CO_3 (1.40 g, 10.2 mmol). The mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the mixture was concentrated in vacuo. The residue was diluted with H_2O (30 mL) and extracted with EtOAc (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–15% EtOAc:petroleum ether) to give 2-[(3-methyloxetan-3-yl)oxy]pyrimidin-5-ol (**Intermediate A-43**). MS = 289.0 / 291.0 $[M+H]^+$.

General Procedure for Intermediate A-44

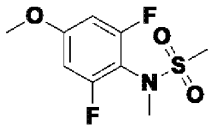


Step 1: *N*-(2,6-difluoro-4-methoxyphenyl)methanesulfonamide



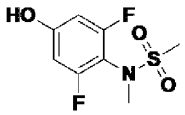
[0712] To a 0 °C mixture of 2,6-difluoro-4-methoxyaniline (3.00 g, 18.9 mmol) and TEA (3.15 mL, 22.6 mmol) in DCM (30 mL) was added methanesulfonic anhydride (8.21 g, 47.1 mmol) dropwise. The mixture was stirred at room temperature for 10 h. The reaction mixture was quenched with H_2O (30 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 40 g cartridge, 0–50% EtOAc:petroleum ether) to give *N*-(2,6-difluoro-4-methoxyphenyl)methanesulfonamide. MS = 236.1 $[M–H]^–$.

Step 2: *N*-(2,6-difluoro-4-methoxyphenyl)-*N*-methylmethanesulfonamide



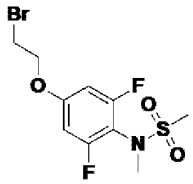
[0713] To a 0 °C solution of *N*-(2,6-difluoro-4-methoxyphenyl)methanesulfonamide (1.00 g, 4.22 mmol) in THF (10 mL) was added NaH (184 mg, 60 wt% in mineral oil, 4.59 mmol). After stirring at 0 °C for 15 min, MeI (2.62 mL, 42.2 mmol) was added. The mixture was stirred at room temperature for 5 h. The reaction mixture was cooled to 0 °C, quenched with H_2O (30 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 0–30% EtOAc:petroleum ether) to give *N*-(2,6-difluoro-4-methoxyphenyl)-*N*-methylmethanesulfonamide. MS = 252.1 $[M+H]^+$.

Step 3: *N*-(2,6-difluoro-4-hydroxyphenyl)-*N*-methylmethanesulfonamide



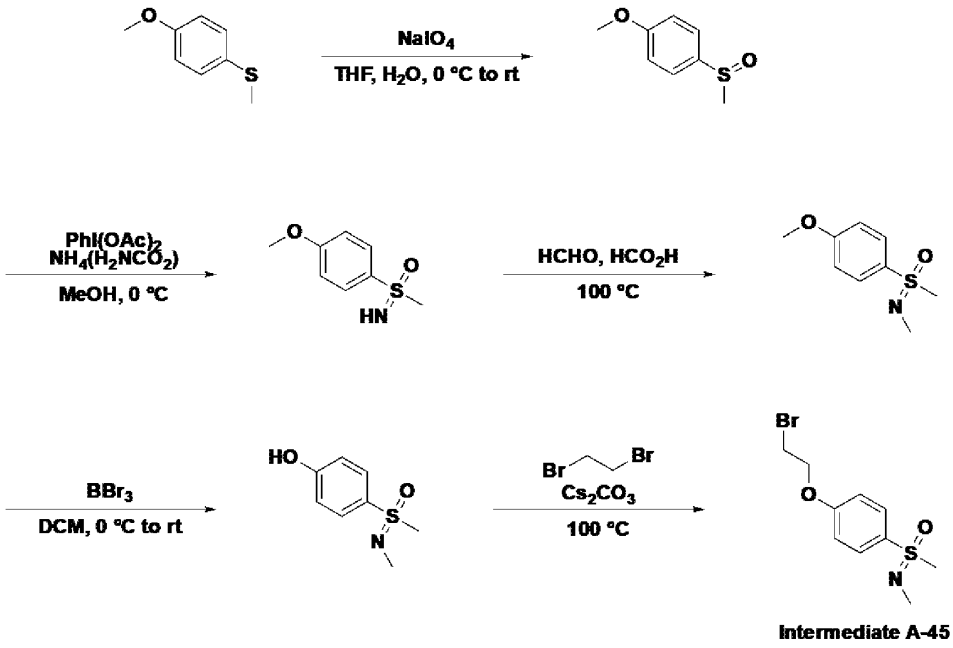
[0714] To a 0 °C solution of *N*-(2,6-difluoro-4-methoxyphenyl)-*N*-methylmethanesulfonamide (786 mg, 3.13 mmol) in DCM (8 mL) was added BBr_3 (0.904 mL, 9.39 mmol) dropwise. The mixture was stirred at room temperature for 6 h. The reaction mixture was cooled to 0 °C and quenched with H_2O (10 mL). The resulting biphasic mixture was concentrated in vacuo to remove DCM and the remaining aqueous phase was adjusted to pH = 8–9 with saturated aqueous $NaHCO_3$. The resulting solid was isolated via filtration and washed with MTBE. The filter cake was dried in vacuo to give *N*-(2,6-difluoro-4-hydroxyphenyl)-*N*-methylmethanesulfonamide. MS = 238.1 $[M+H]^+$.

Step 4: N-[4-(2-bromoethoxy)-2,6-difluorophenyl]-N-methylmethanesulfonamide

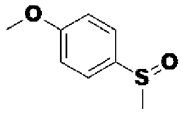


[0715] To a solution of *N*-(2,6-difluoro-4-hydroxyphenyl)-*N*-methylmethanesulfonamide (710 mg, 2.99 mmol) in 1,2-dibromoethane (10 mL) was added Cs_2CO_3 (1.95 g, 5.99 mmol). The mixture was stirred at 100 °C for 4 h. The reaction mixture was cooled to 0 °C, quenched with H_2O (20 mL), and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 0–30% EtOAc:petroleum ether) to give *N*-[4-(2-bromoethoxy)-2,6-difluorophenyl]-*N*-methylmethanesulfonamide (**Intermediate A-44**). MS = 361.1 / 363.1 $[M+NH_4]^+$.

General Procedure for Intermediate A-45



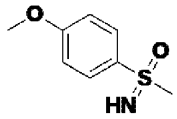
Step 1: 1-methanesulfinyl-4-methoxybenzene



[0716] To a 0 °C solution of 1-methoxy-4-(methylsulfanyl)benzene (15.3 mL, 110 mmol) in THF (160 mL) and H_2O (160 mL) was added $NaIO_4$ (12.2 mL, 220 mmol) portionwise. The mixture was allowed to warm to room temperature and stirred for 16 h, and then solids were removed by

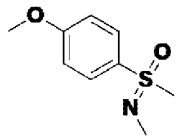
filtration. The filtrate was cooled to 0 °C, quenched with saturated aqueous Na_2SO_3 solution (200 mL), and extracted with EtOAc (5 x 200 mL). The combined organic layers were washed with saturated aqueous Na_2SO_3 solution (2 x 200 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give 1-methanesulfinyl-4-methoxybenzene, which was used in the subsequent step without further purification. MS = 171.1 $[M+H]^+$.

Step 2: imino(4-methoxyphenyl)methyl-λ⁶-sulfanone



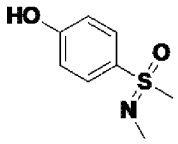
[0717] To a 0 °C solution of 1-methanesulfinyl-4-methoxybenzene (110 mmol) and $PhI(OAc)_2$ (15 g, 470 mmol) in MeOH (200 mL) was added ammonium carbamate (13.8 g, 176 mmol). The mixture was stirred at 0 °C for 1 h, and then was concentrated in vacuo. The residue was diluted with H_2O (100 mL) and adjusted to pH = 6–7 with the dropwise addition of saturated aqueous Na_2CO_3. Solids were removed by filtration, and the filtrate was extracted with EtOAc (5 x 200 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 330 g cartridge, 80–100% EtOAc:petroleum ether) to give imino(4-methoxyphenyl)methyl-λ⁶-sulfanone. MS = 186.1 $[M+H]^+$.

Step 3: [(4-methoxyphenyl)(methyl)oxo-λ⁶-sulfanylidene](methyl)amine



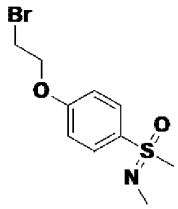
[0718] A solution of imino(4-methoxyphenyl)methyl-λ⁶-sulfanone (10.0 g, 54.0 mmol) and formaldehyde aqueous solution (29.7 mL, 37 wt%, 1.08 mol) in formic acid (100 mL) was stirred at 100 °C for 30 h. The mixture was cooled to 0 °C and then diluted with H_2O (120 mL). The solution was adjusted to pH = 6–7 with the dropwise addition of 5.0 M aqueous NaOH. The mixture was extracted with EtOAc (3 x 120 mL). The combined organic layers were washed with brine (80 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give [(4-methoxyphenyl)(methyl)oxo-λ⁶-sulfanylidene](methyl)amine, which was used in the subsequent step without further purification. MS = 200.2 $[M+H]^+$.

Step 4: 4-[methyl(methylimino)oxo-λ⁶-sulfanyl]phenol



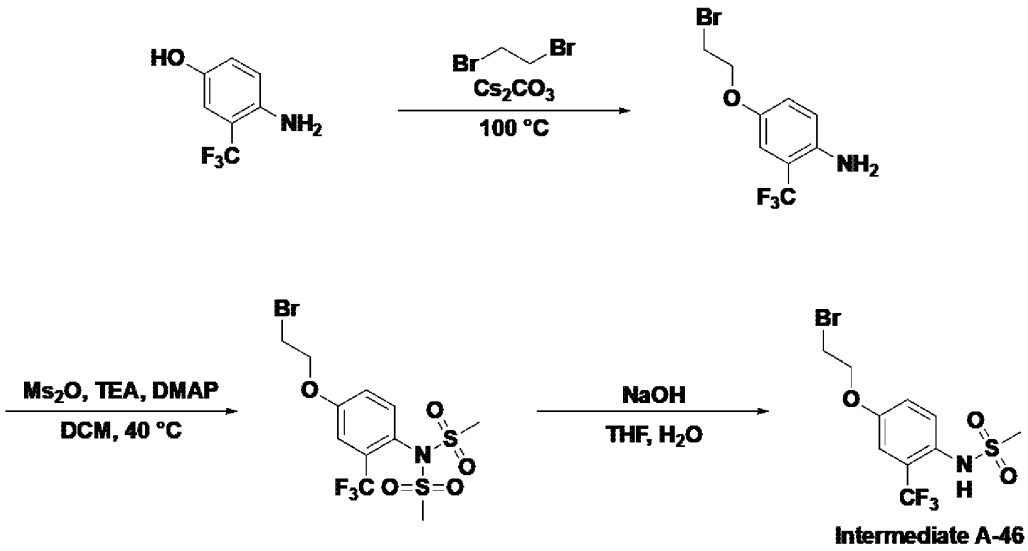
[0719] To a 0 °C solution of [(4-methoxyphenyl)(methyl)oxo-λ⁶-sulfanylidene](methyl)amine (11.0 g, 55.2 mmol) in DCM (120 mL) was added BBr_3 (21.3 mL, 221 mmol). The mixture was stirred at room temperature for 2 h, then was cooled to 0 °C and quenched by the addition of H_2O (15 mL). The solution was adjusted to pH = 6–8 with the dropwise addition of saturated aqueous $NaHCO_3$. The resulting solids were removed by filtration and the filter cake was washed with THF (3 x 200 mL). The resulting filtrate was concentrated in vacuo, and the resulting residue was triturated with a 1:1 mixture of petroleum ether and EtOAc, then dried in vacuo to give 4-[methyl(methylimino)oxo-λ⁶-sulfanyl]phenol. MS =186.0 $[M+H]^+$.

Step 5: {[4-(2-bromoethoxy)phenyl](methyl)oxo-λ⁶-sulfanylidene}(methyl)amine



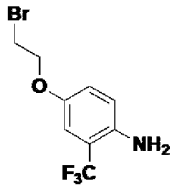
[0720] To a mixture of 4-[methyl(methylimino)oxo-λ⁶-sulfanyl]phenol (900 mg, 4.86 mmol) and 1,2-dibromoethane (10.0 mL, 133 mmol) was added Cs_2CO_3 (3.17 g, 9.72 mmol). The mixture was stirred at 100 °C for 16 h. After cooling to room temperature, solids were removed via filtration and the filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 0–50% EtOAc:petroleum ether) to give {[4-(2-bromoethoxy)phenyl](methyl)oxo-λ⁶-sulfanylidene}(methyl)amine (**Intermediate A-45**). MS = 291.9 / 293.9 $[M+H]^+$.

General Procedure for Intermediate A-46



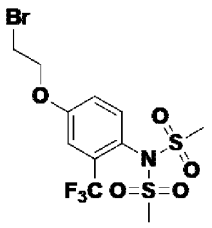
Intermediate A-46

Step 1: 4-(2-bromoethoxy)-2-(trifluoromethyl) aniline



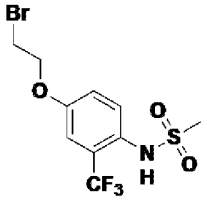
[0721] To a solution 4-amino-3-(trifluoromethyl)phenol (3.00 g, 16.9 mmol) in 1,2-dibromoethane (30 mL, 399 mmol) was added Cs_2CO_3 (16.6 g, 50.8 mmol). The mixture was stirred at 100 °C for 12 h. After cooling to room temperature, the mixture was filtered and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 40 g cartridge, 0–50% EtOAc:petroleum ether) to give 4-(2-bromoethoxy)-2-(trifluoromethyl) aniline. MS = 284.0 / 286.0 $[M+H]^+$.

Step 2: *N*-[4-(2-bromoethoxy)-2-(trifluoromethyl)phenyl]-*N*-methanesulfonylmethanesulfonamide



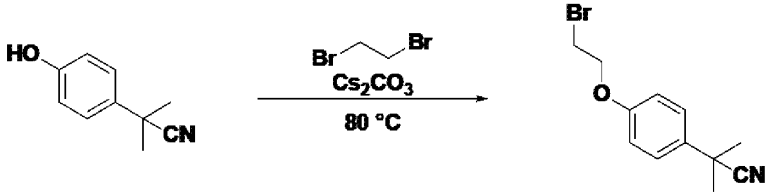
[0722] To a solution of 4-(2-bromoethoxy)-2-(trifluoromethyl) aniline (600 mg, 2.11 mmol) in DCM (10 mL) was added methanesulfonic anhydride (736 mg, 4.22 mmol), TEA (0.882 mL, 6.34 mmol) and DMAP (25.8 mg, 0.211 mmol). The mixture was stirred at 40 °C for 16 h. After cooling to temperature, the reaction mixture was quenched with H_2O (20 mL), and then extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–50% EtOAc:petroleum ether) to give *N*-[4-(2-bromoethoxy)-2-(trifluoromethyl)phenyl]-*N*-methanesulfonylmethanesulfonamide.

Step 3: *N*-[4-(2-bromoethoxy)-2-(trifluoromethyl)phenyl]methanesulfonamide



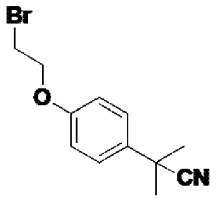
[0723] To a solution of *N*-[4-(2-bromoethoxy)-2-(trifluoromethyl)phenyl]-*N*-methanesulfonylmethanesulfonamide (521 mg, 1.18 mmol) in THF (6 mL) was added a solution of NaOH (237 mg, 5.92 mmol) in H_2O (1.5 mL). The mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with H_2O (10 mL), and then extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give *N*-[4-(2-bromoethoxy)-2-(trifluoromethyl)phenyl]methanesulfonamide (**Intermediate A-46**). MS = 359.9 / 362.0 $[M–H]^-$.

General Procedure for Intermediate A-47



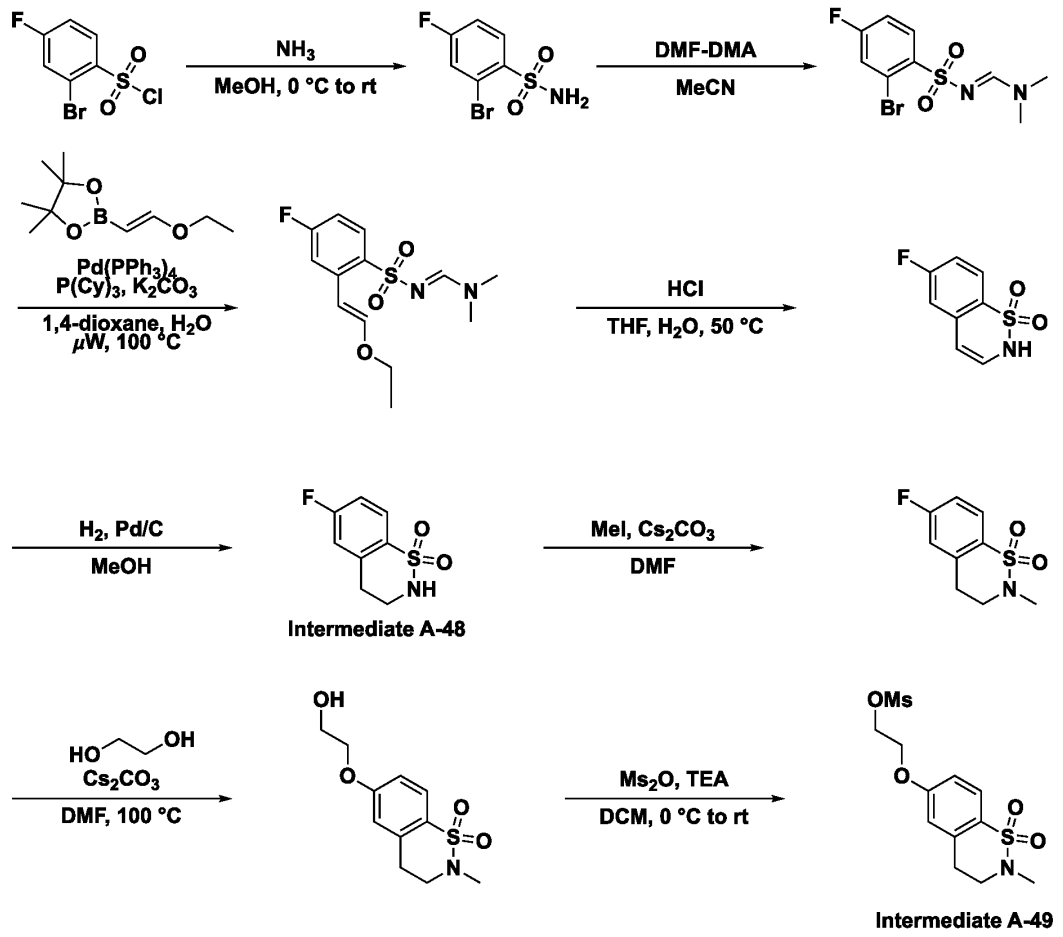
Intermediate A-47

Step 1: 2-[4-(2-bromoethoxy)phenyl]-2-methylpropanenitrile

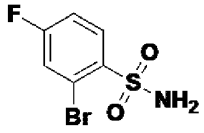


[0724] To a solution of 2-(4-hydroxyphenyl)-2-methylpropanenitrile (500 mg, 3.10 mmol) in 1,2-dibromoethane (8.0 mL, 106 mmol) was added Cs_2CO_3 (3.03 g, 9.31 mmol). The mixture was stirred at 100 °C for 12 h. After cooling to room temperature, the mixture was filtered to remove solids, and the resulting filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 0–50% EtOAc:petroleum ether) to give 2-[4-(2-bromoethoxy)phenyl]-2-methylpropanenitrile (**Intermediate A-47**) . MS = 241.1 / 243.0 $[M–CN]^+$.

General Procedure for Intermediates A-48 & A-49



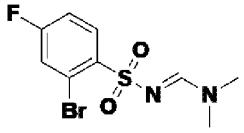
Step 1: 2-bromo-4-fluorobenzene-1-sulfonamide



[0725] A solution of 2-bromo-4-fluorobenzene-1-sulfonyl chloride (1.07 mL, 7.31 mmol) in MeOH (30 mL) was cooled to 0 °C and NH_3 was bubbled into the reaction mixture over a period of 15 min. The reaction mixture was warmed to room temperature and stirred for 16 h. The mixture was concentrated in vacuo and diluted with H_2O (100 mL). The reaction mixture was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and

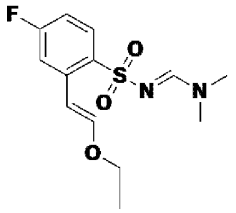
concentrated in vacuo give 2-bromo-4-fluorobenzene-1-sulfonamide, which was used in the subsequent step without further purification.

Step 2: *N*'-(2-bromo-4-fluorobenzenesulfonyl)-*N,N*-dimethylmethanimidamide



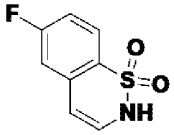
[0726] To a mixture of 2-bromo-4-fluorobenzene-1-sulfonamide (1.00 g, 3.94 mmol) in MeCN (10 mL) was added a solution *N,N*-dimethylformamide dimethyl acetal (0.627 mL, 4.72 mmol) in MeCN (1 mL). The mixture was stirred at room temperature for 1 h, and was then concentrated in vacuo to give *N*'-(2-bromo-4-fluorobenzenesulfonyl)-*N,N*-dimethylmethanimidamide, which was used in the subsequent step without further purification. MS = 309.0 / 311.0 $[M+H]^+$.

Step 3: *N*'-{2-[(1E)-2-ethoxyethenyl]-4-fluorobenzenesulfonyl}-*N,N*-dimethylmethanimidamide



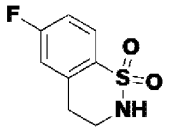
[0727] A solution of 2-[(1E)-2-ethoxyethenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (895 mg, 4.52 mmol), *N*'-(2-bromo-4-fluorobenzenesulfonyl)-*N,N*-dimethylmethanimidamide (700 mg, 2.26 mmol), K_2CO_3 (937 mg, 6.78 mmol), $Pd(PPh_3)_4$ (261 mg, 0.226 mmol), and PCy_3 (73.3 μL, 0.226 mmol) in 1,4-dioxane (5 mL) and H_2O (0.5 mL) was purged with N_2 (2x) and heated via microwave for 1 h at 100 °C. After cooling to room temperature, the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 10 g cartridge, 0–30% EtOAc:petroleum ether) to give *N*'-{2-[(1E)-2-ethoxyethenyl]-4-fluorobenzenesulfonyl}-*N,N*-dimethylmethanimidamide. MS = 301.1 $[M+H]^+$.

Step 4: 6-fluoro-2H-1λ⁶,2-benzothiazine-1,1-dione



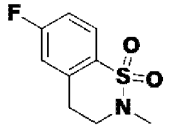
[0728] A solution of *N*'-{2-[(1E)-2-ethoxyethenyl]-4-fluorobenzenesulfonyl}-*N*,*N*-dimethylmethanimidamide (500 mg, 1.66 mmol) in 6.0 M aqueous HCl (2.77 mL, 16.6 mmol) and THF (5 mL) was stirred at 50 °C for 16 h. After cooling to room temperature, the mixture was concentrated in vacuo. The residue was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give 6-fluoro-2H-1λ⁶,2-benzothiazine-1,1-dione, which was used in the subsequent step without further purification. MS = 198.1 $[M–H]^-$.

Step 5: 6-fluoro-3,4-dihydro-2H-1λ⁶,2-benzothiazine-1,1-dione



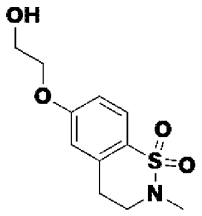
[0729] To a mixture of Pd/C (10.0 mg, 10 wt%, 0.0094 mmol) in MeOH (3 mL) was added 6-fluoro-2H-1λ⁶,2-benzothiazine-1,1-dione (50.0 mg, 0.251 mmol). The mixture was purged with H_2 (2x). The mixture was stirred at room temperature for 16 h under an atmosphere of H_2 (15 psi). The reaction mixture filtered through celite, and the filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 4 g cartridge, 0–50% EtOAc:petroleum ether) to give 6-fluoro-3,4-dihydro-2H-1λ⁶,2-benzothiazine-1,1-dione (**Intermediate A-48**). MS = 200.0 $[M–H]^-$.

Step 6: 6-fluoro-2-methyl-3,4-dihydro-2H-1λ⁶,2-benzothiazine-1,1-dione



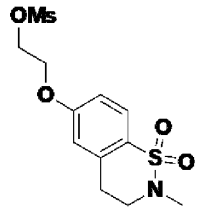
[0730] To a solution of 6-fluoro-3,4-dihydro-2H-1λ⁶,2-benzothiazine-1,1-dione (500 mg, 2.48 mmol) and Cs_2CO_3 (891 mg, 2.73 mmol) in DMF (10 mL) was added MeI (1.55 mL, 24.9 mmol). The mixture was stirred at room temperature for 3 h and was then diluted with H_2O (10 mL). The mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (2 x 5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give 6-fluoro-2-methyl-3,4-dihydro-2H-1λ⁶,2-benzothiazine-1,1-dione, which was used in the subsequent step without further purification. MS = 216.1 $[M+H]^+$.

Step 7: 6-(2-hydroxyethoxy)-2-methyl-3,4-dihydro-2H-1λ⁶,2-benzothiazine-1,1-dione



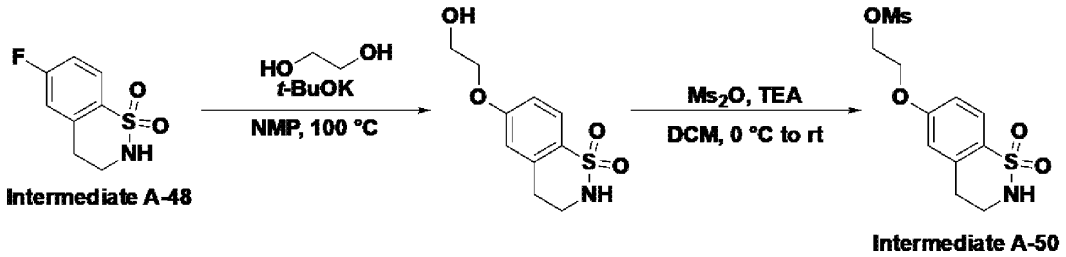
[0731] A solution of 6-fluoro-2-methyl-3,4-dihydro-2H-1λ⁶,2-benzothiazine-1,1-dione (700 mg, 3.25 mmol), ethylene glycol (1.82 mL, 32.5 mmol) and Cs_2CO_3 (3.18 g, 9.76 mmol) in DMF (3 mL) was stirred at 100 °C for 5 h. After cooling to room temperature, the mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (2 x 5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 4 g cartridge, 0–60% EtOAc:petroleum ether) to give 6-(2-hydroxyethoxy)-2-methyl-3,4-dihydro-2H-1λ⁶,2-benzothiazine-1,1-dione. MS = 258.0 $[M+H]^+$.

Step 8: 2-[(2-methyl-1,1-dioxo-3,4-dihydro-2H-1λ⁶,2-benzothiazin-6-yl)oxy]ethyl methanesulfonate

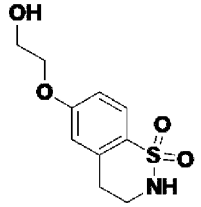


[0732] To a 0 °C solution of 6-(2-hydroxyethoxy)-2-methyl-3,4-dihydro-2H-1λ⁶,2-benzothiazine-1,1-dione (180 mg, 0.700 mmol) and TEA (0.146 mL, 1.05 mmol) in DCM (5 mL) was added methanesulfonic anhydride (146 mg, 0.839 mmol). After stirring at 0 °C for 1 h, the reaction mixture was quenched with H_2O (3 mL). The solution was adjusted to pH = 6 with the dropwise addition of 2.0 M aqueous HCl. The mixture was extracted with DCM (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give 2-[(2-methyl-1,1-dioxo-3,4-dihydro-2H-1λ⁶,2-benzothiazin-6-yl)oxy]ethyl methanesulfonate, which was used in the subsequent step without further purification (**Intermediate A-49**). MS = 336.1 $[M+H]^+$.

General Procedure for Intermediate A-50

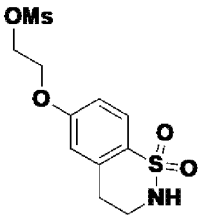


Step 1: 6-(2-hydroxyethoxy)-3,4-dihydro-2H-1λ⁶,2-benzothiazine-1,1-dione



[0733] A solution of 6-fluoro-3,4-dihydro-2H-1λ⁶,2-benzothiazine-1,1-dione (**Intermediate A-48**, 2.50 g, 12.4 mmol), ethylene glycol (3.47 mL, 62.1 mmol) and *t*-BuOK (6.97 g, 62.1 mmol) in NMP (15 mL) was stirred at 100 °C for 16 h. After cooling to room temperature, the reaction was quenched with H_2O (30 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 0–100% EtOAc:petroleum ether) to give 6-(2-hydroxyethoxy)-3,4-dihydro-2H-1λ⁶,2-benzothiazine-1,1-dione. MS = 242.1 $[M–H]^-$.

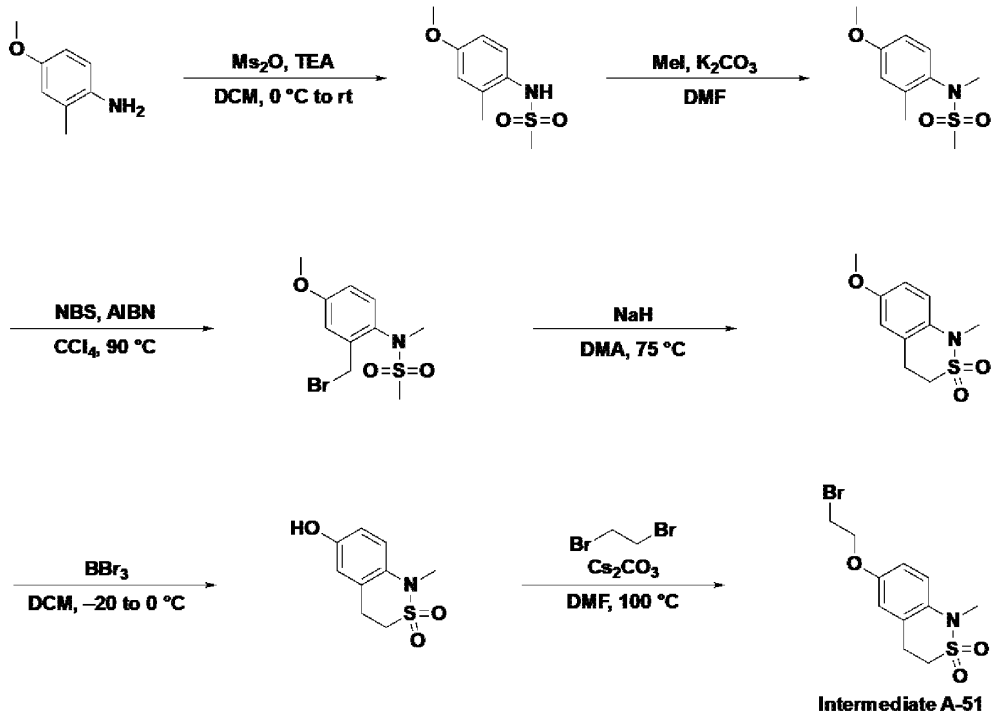
Step 2: 2-[(1,1-dioxo-3,4-dihydro-2H-1λ⁶,2-benzothiazin-6-yl)oxy]ethyl methanesulfonate



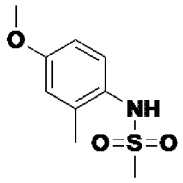
[0734] To a 0 °C solution of 6-(2-hydroxyethoxy)-3,4-dihydro-2H-1λ⁶,2-benzothiazine-1,1-dione (400 mg, 1.64 mmol) and TEA (0.343 mL, 2.47 mmol) in DCM (5 mL) was added methanesulfonic anhydride (344 mg, 1.97 mmol). After stirring at 0 °C for 1 h, the reaction mixture was quenched with H_2O (3 mL). The solution was adjusted to pH = 6 with the dropwise addition of 2.0 M aqueous HCl. The mixture was extracted with DCM (3 x 5 mL). The combined organic layers

were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 4 g cartridge, 0–80% EtOAc:petroleum ether) to give 2-[(1,1-dioxo-3,4-dihydro-2H-1λ⁶,2-benzothiazin-6-yl)oxy]ethyl methanesulfonate (**Intermediate A-50**). MS = 320.1 $[M–H]^+$.

General Procedure for Intermediate A-51



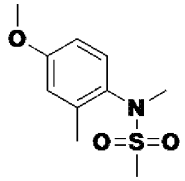
Step 1: *N*-(4-methoxy-2-methylphenyl)methanesulfonamide



[0735] To a 0 °C solution of 4-methoxy-2-methylaniline (7.41 mL, 58.3 mmol) and TEA (12.2 mL, 87.4 mmol) in DCM (50 mL) was added methanesulfonic anhydride (11.2 g, 64.2 mmol). After stirring at room temperature for 1 h, the reaction mixture was quenched with H_2O (35 mL). The solution was adjusted to pH = 6 with the dropwise addition of 1.0 M aqueous HCl. The mixture was extracted with DCM (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered,

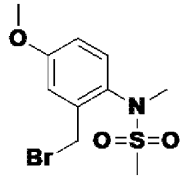
and concentrated in vacuo. The crude product was triturated with EtOAc, and the solid was isolated via filtration then concentrated in vacuo to give *N*-(4-methoxy-2-methylphenyl)methanesulfonamide. MS = 214.2 $[M–H]^-$.

Step 2: *N*-(4-methoxy-2-methylphenyl)-N-methylmethanesulfonamide



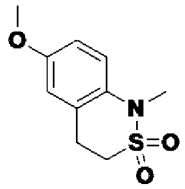
[0736] A solution of N-(4-methoxy-2-methylphenyl)methanesulfonamide (10.0 g, 46.5 mmol), MeI (4.34 mL, 69.68 mmol) and K_2CO_3 (12.8 g, 92.9 mmol) in DMF (30 mL) was stirred at for 2 h. The reaction mixture was quenched with H_2O (15 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give *N*-(4-methoxy-2-methylphenyl)-*N*-methylmethanesulfonamide, which was used in the subsequent step without further purification.

Step 3: *N*-[2-(bromomethyl)-4-methoxyphenyl]-N-methylmethanesulfonamide



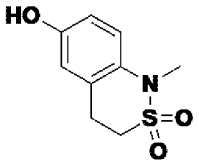
[0737] A solution *N*-(4-methoxy-2-methylphenyl)-N-methylmethanesulfonamide (5.00 g, 21.8 mmol), NBS (4.66 g, 26.2 mmol) and AIBN (71.6 mg, 0.436 mmol) in CCl_4 (50 mL) was stirred at 90 °C for 2 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 40 g cartridge, 0–80% EtOAc:petroleum ether) to give *N*-[2-(bromomethyl)-4-methoxyphenyl]-*N*-methylmethanesulfonamide. MS = 308.0 / 310.0 $[M+H]^+$.

Step 4: 6-methoxy-1-methyl-3,4-dihydro-1H-2λ⁶,1-benzothiazine-2,2-dione



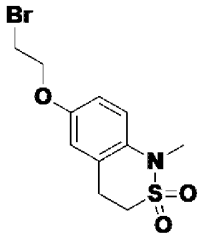
[0738] To a 0 °C solution of *N*-[2-(bromomethyl)-4-methoxyphenyl]-*N*-methylmethanesulfonamide (2.60 g, 8.44 mmol) in DMA (15 mL) was added NaH (371 mg, 60 wt% in mineral oil, 9.28 mmol) in portions. The mixture was stirred at 75 °C for 4 h. After cooling to room temperature, the reaction was quenched with H_2O (20 mL). The mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–30% EtOAc:petroleum ether) to give 6-methoxy-1-methyl-3,4-dihydro-1H-2λ⁶,1-benzothiazine-2,2-dione. MS = 228.1 $[M+H]^+$.

Step 5: 6-hydroxy-1-methyl-3,4-dihydro-1H-2λ⁶,1-benzothiazine-2,2-dione



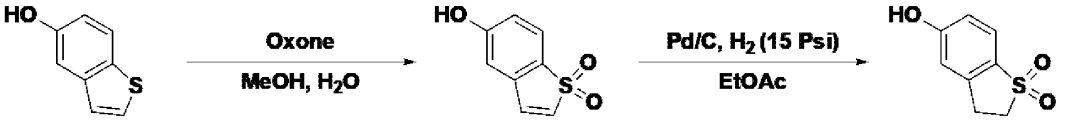
[0739] To a –20 °C solution of 6-methoxy-1-methyl-3,4-dihydro-1H-2λ⁶,1-benzothiazine-2,2-dione (1.20 g, 5.28 mmol) in DCM (15 mL) was added BBr_3 (1.53 mL, 15.8 mmol) dropwise. The mixture was warmed to 0 °C and stirred for 1 h. The reaction mixture was quenched by the addition of H_2O (15 mL), warmed to room temperature, and then adjusted to pH = 8 with saturated aqueous $NaHCO_3$. The mixture was extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 10 g cartridge, 0–30% EtOAc:petroleum ether) to give 6-hydroxy-1-methyl-3,4-dihydro-1H-2λ⁶,1-benzothiazine-2,2-dione. MS = 212.1 $[M–H]^-$.

Step 6: 6-(2-bromoethoxy)-1-methyl-3,4-dihydro-1H-2λ⁶,1-benzothiazine-2,2-dione



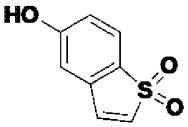
[0740] A solution of 1,2-dibromoethane (1.59 mL, 21.1 mmol), 6-hydroxy-1-methyl-3,4-dihydro-1H-2λ⁶,1-benzothiazine-2,2-dione (900 mg, 4.22 mmol) and Cs_2CO_3 (2.06 g, 6.33 mmol) in DMF (2 mL) was stirred at 100 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (15 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 10 g cartridge, 0–30% EtOAc:petroleum ether) to give 6-(2-bromoethoxy)-1-methyl-3,4-dihydro-1H-2λ⁶,1-benzothiazine-2,2-dione (**Intermediate A-51**). MS = 319.9 / 321.9 $[M+H]^+$.

General Procedure for Intermediate A-52



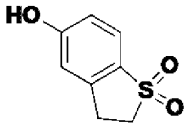
Intermediate A-52

Step 1: 5-hydroxy-1λ⁶-benzothiophene-1,1-dione



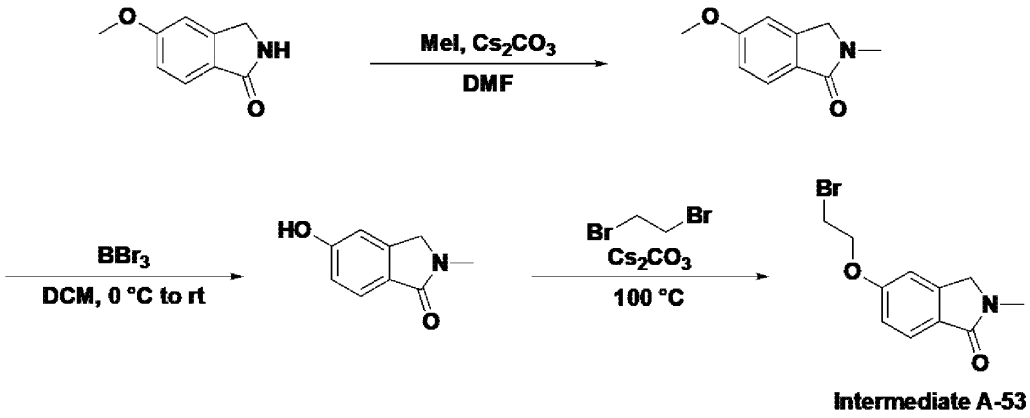
[0741] To a 0 °C solution of Oxone (1.84 g, 3.00 mmol) in H_2O (15 mL) was added a solution of 1-benzothiophen-5-ol (300 mg, 2.00 mmol) in MeOH (15 mL) dropwise. The mixture was stirred at room temperature for 6 h. The reaction mixture was concentrated in vacuo, diluted with H_2O (10 mL), and then extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–50% EtOAc:petroleum ether) to give 5-hydroxy-1λ⁶-benzothiophene-1,1-dione. MS = 181.1 $[M-H]^-$.

Step 2: 5-hydroxy-2,3-dihydro-1λ⁶-benzothiophene-1,1-dione



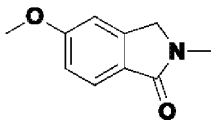
[0742] To a solution of 5-hydroxy-1λ⁶-benzothiophene-1,1-dione (270 mg, 1.48 mmol) in EtOAc (30 mL) was added Pd/C (27 mg, 10 wt%, 0.025 mmol) under N_2 atmosphere. The mixture was purged with H_2 (3x). The mixture was stirred at room temperature for 3 h under an atmosphere of H_2 (15 psi). The reaction mixture filtered through Celite, and the filtrate was concentrated in vacuo to give 5-hydroxy-2,3-dihydro-1λ⁶-benzothiophene-1,1-dione (**Intermediate A-52)**, which was used in the subsequent step without further purification. MS = 183.1 $[M–H]^-$.

General Procedure for Intermediate A-53



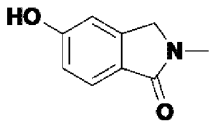
Intermediate A-53

Step 1: 5-methoxy-2-methyl-2,3-dihydro-1H-isoindol-1-one



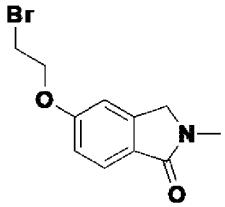
[0743] To a solution of 5-methoxy-2,3-dihydro-1H-isoindol-1-one (750 mg, 4.60 mmol,) in DMF (15 mL) were added Cs_2CO_3 (2.25 g, 6.89 mmol) and MeI (0.343 mL, 5.52 mmol). The mixture was stirred at room temperature for 16 h. The mixture was filtered to remove solids, and the resulting filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 25 g cartridge, 50–100% EtOAc:petroleum ether) to give 5-methoxy-2-methyl-2,3-dihydro-1H-isoindol-1-one. MS = 178.0 $[M+H]^+$.

Step 2: 5-hydroxy-2-methyl-2,3-dihydro-1H-isoindol-1-one



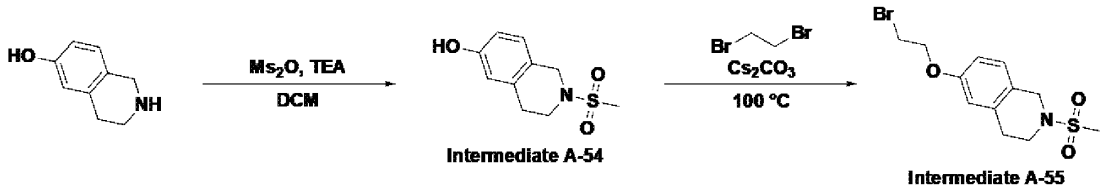
[0744] To a 0 °C solution of 5-methoxy-2-methyl-2,3-dihydro-1H-isoindol-1-one (800 mg, 4.51 mmol) in DCM (10 mL) was added BBr_3 (1.31 mL, 13.5 mmol). The mixture was stirred at room temperature for 2 h. The reaction mixture was cooled to 0 °C and quenched by the addition of MeOH (5 mL), and then concentrated in vacuo. The crude residue was triturated with EtOAc to give 5-hydroxy-2-methyl-2,3-dihydro-1H-isoindol-1-one, which was taken to the next step without further purification. MS = 164.0 $[M+H]^+$.

Step 3: 5-(2-bromoethoxy)-2-methyl-2,3-dihydro-1H-isoindol-1-one

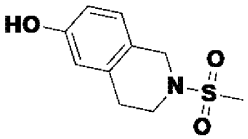


[0745] To a solution of 5-hydroxy-2-methyl-2,3-dihydro-1H-isoindol-1-one (1.25 g, 7.66 mmol) in 1,2-dibromoethane (12.5 mL, 166 mmol) was added Cs_2CO_3 (4.99 g, 15.3 mmol). The mixture was stirred at 100 °C for 16 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 25 g cartridge, 70–100% EtOAc:petroleum ether) to give 5-(2-bromoethoxy)-2-methyl-2,3-dihydro-1H-isoindol-1-one (**Intermediate A-53**). MS = 270.0 / 272.0 $[M+H]^+$.

General Procedure for Intermediates A-54 & A-55

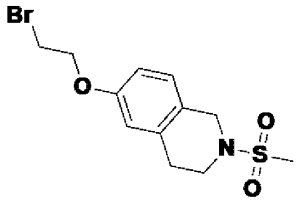


Step 1: 2-methanesulfonyl-1,2,3,4-tetrahydroisoquinolin-6-ol



[0746] A mixture of 1,2,3,4-tetrahydroisoquinolin-6-ol (500 mg, 3.35 mmol), methanesulfonic anhydride (1.17 g, 6.70 mmol), and TEA (0.933 mL, 6.70 mmol) in DCM (10 mL) was degassed and purged with N_2 (3x). After stirring at room temperature for 3 h under N_2 atmosphere, the reaction mixture was quenched with H_2O (5 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–50% EtOAc:petroleum ether) to give 2-methanesulfonyl-1,2,3,4-tetrahydroisoquinolin-6-ol (**Intermediate A-54**). MS = 228.1 $[M+H]^+$.

Step 2: 6-(2-bromoethoxy)-2-methanesulfonyl-1,2,3,4-tetrahydroisoquinoline

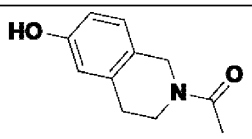


[0747] To a solution of 2-methanesulfonyl-1,2,3,4-tetrahydroisoquinolin-6-ol (100 mg, 0.440 mmol) in 1,2-dibromoethane (5 mL) was added Cs_2CO_3 (430 mg, 1.32 mmol). The mixture was stirred at 100 °C for 5 h. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 4 g cartridge, 0–100% EtOAc:petroleum ether) to give 6-(2-bromoethoxy)-2-methanesulfonyl-1,2,3,4-tetrahydroisoquinoline (**Intermediate A-55**). MS = 334.1 / 336.1 $[M+H]^+$.

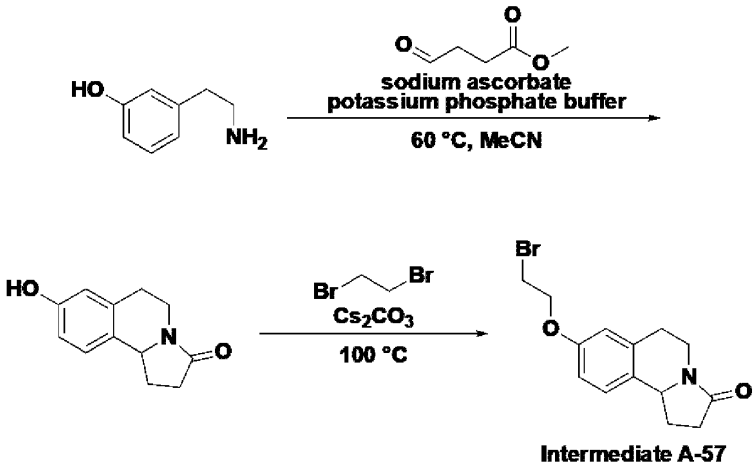
[0748] The following intermediate in Table 9 was prepared using procedures similar to Step 1 described for **Intermediate A-54**, using the appropriate starting materials.

General Procedure for Intermediate A-56

Table 9.

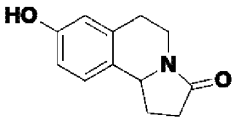
Intermediate #	Structure	Name	Exact Mass $[M+H]^+$
A-56		1-(6-hydroxy-1,2,3,4-tetrahydroisoquinolin-2-yl)ethan-1-one	Calc'd 192.1 Found 192.2

General Procedure for Intermediate A-57



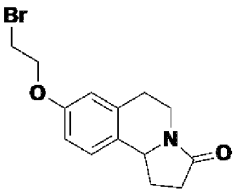
Intermediate A-57

Step 1: 8-hydroxy-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinolin-3-one



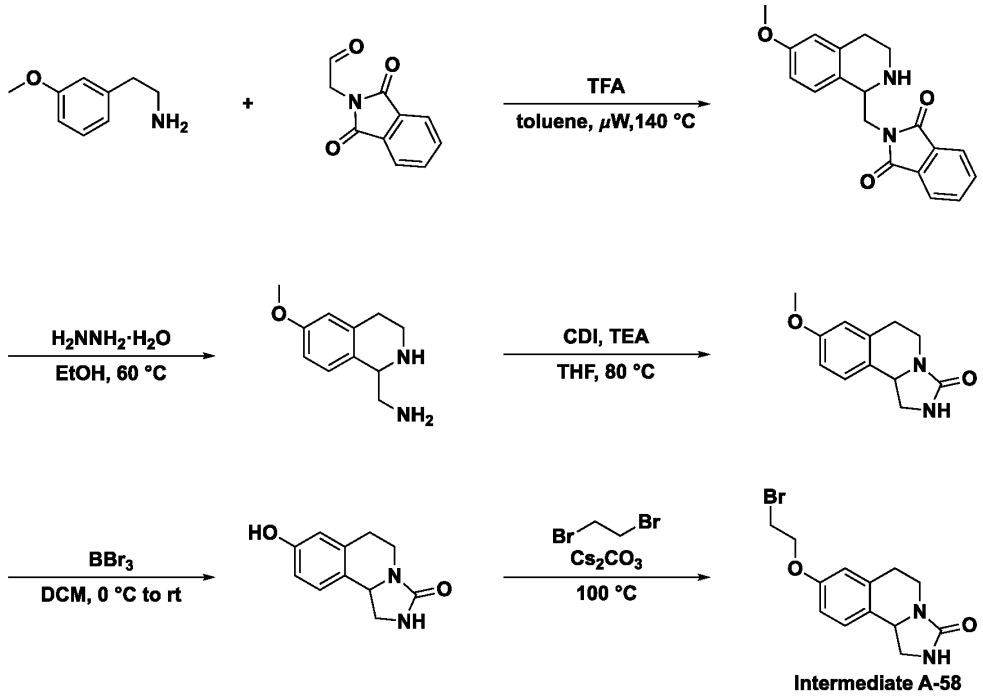
[0749] A mixture of 3-(2-aminoethyl)phenol (1.00 g, 5.76 mmol, HCl salt), methyl 4-oxobutanoate (1.00 g, 8.64 mmol), and sodium ascorbate (1.14 g, 5.76 mmol) in a solution of 0.3 M aqueous potassium phosphate buffer (200 mL) and MeCN (200 mL) was stirred at 60 °C for 18 h under an atmosphere of N_2. 1.0 M aqueous Na_2CO_3 (2.0 mL, 2.0 mmol) was added, and the mixture was stirred for another 4 h at 60 °C. After cooling to room temperature, the mixture was extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 40 g cartridge, 0–100% EtOAc:petroleum ether to 0–10% MeOH:EtOAc) to give 8-hydroxy-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinolin-3-one. MS = 204.1 $[M+H]^+$.

Step 2: 8-(2-bromoethoxy)-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinolin-3-one

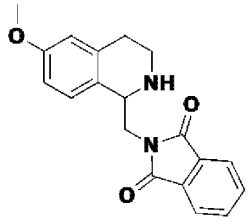


[0750] To a solution of 8-hydroxy-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinolin-3-one (300 mg, 1.48 mmol) in 1,2-dibromoethane (5.00 mL, 66.3 mmol) was added Cs_2CO_3 (962 mg, 2.95 mmol). The mixture was stirred at 100 °C for 32 h. After cooling to room temperature, the reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (4 x 8 mL). The combined organic layers were washed with brine (2 x 8 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 25 g cartridge, 70–100% EtOAc:petroleum ether) to give 8-(2-bromoethoxy)-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinolin-3-one (**Intermediate A-57**). MS = 310.0 / 312.0 $[M+H]^+$.

General Procedure for Intermediate A-58

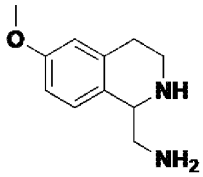


Step 1: 2-[(6-methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]-2,3-dihydro-1H-isoindole-1,3-dione



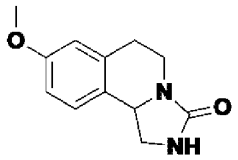
[0751] A mixture of 2-(3-methoxyphenyl)ethan-1-amine (4.85 mL, 33.1 mmol), 2-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)acetaldehyde (7.51 g, 39.7 mmol), and TFA (19.6 mL, 265 mmol) in toluene (50 mL) heated via microwave for 30 min at 140 °C under N_2 atmosphere. After cooling to room temperature, the mixture was diluted with H_2O (60 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 80 g cartridge, 0–50% EtOAc:petroleum ether) to give 2-[(6-methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]-2,3-dihydro-1H-isoindole-1,3-dione. MS = 323.2 $[M+H]^+$.

Step 2: 1-(6-methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methanamine



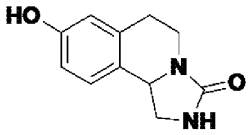
[0752] A mixture of 2-[(6-methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]-2,3-dihydro-1H-isoindole-1,3-dione (5.00 g, 15.5 mmol), $H_2NNH_2 \cdot H_2O$ (2.66 mL, 85% purity, 46.53 mmol) in EtOH (50 mL) was degassed and purged with N_2 (3x). The mixture was stirred at 60 °C for 5 h under N_2 atmosphere. After cooling to room temperature, the mixture was filtered to remove solids, and the resulting filtrate was concentrated in vacuo to give 1-(6-methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methanamine, which was used in the subsequent step without further purification. MS = 193.2 $[M+H]^+$.

Step 3: 8-methoxy-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-3-one



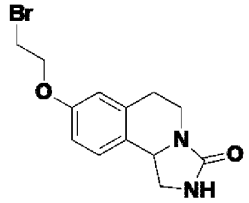
[0753] To a solution of 1-(6-methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methanamine (1.00 g, 5.20 mmol) in THF (20 mL) were added CDI (4.22 g, 26.0 mmol) and TEA (0.724 mL, 5.20 mmol). A total of 5 identical reactions were set up using the described procedure. The mixtures were stirred at 80 °C for 12 h. After cooling to room temperature, the 5 reaction mixtures were combined into one solution and diluted with H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 80 g cartridge, 0–60% EtOAc:petroleum ether) to give 8-methoxy-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-3-one. MS = 219.2 $[M+H]^+$.

Step 4: 8-hydroxy-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-3-one



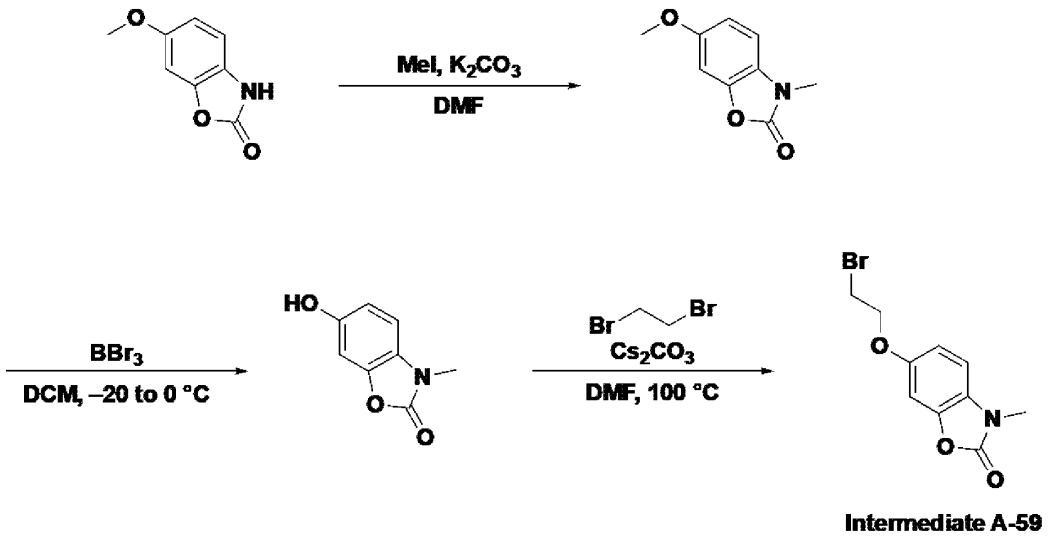
[0754] To a 0 °C solution of 8-methoxy-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-3-one (1.00 g, 4.58 mmol) in DCM (10 mL) was added BBr_3 (0.883 mL, 9.16 mmol) dropwise. The mixture was allowed to warm to room temperature and stirred for 2 h. The mixture was quenched with H_2O (20 mL), then filtered, and the filtrate was concentrated in vacuo to give 8-methoxy-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-3-one, which was used in the subsequent step without further purification. MS = 205.1 $[M+H]^+$.

Step 5: 8-(2-bromoethoxy)-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-3-one



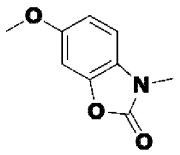
[0755] A mixture of 8-methoxy-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-3-one (700 mg, 3.43 mmol) and Cs_2CO_3 (3.19 g, 9.79 mmol) in 1,2-dibromoethane (15 mL, 197 mmol) was degassed and purged with N_2 (3x).The mixture was stirred at 100 °C for 12 h under N_2 atmosphere. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 40 g cartridge, 0–100% EtOAc:petroleum ether) to give 8-(2-bromoethoxy)-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-3-one (**Intermediate A-58**). MS = 311.1 / 313.1 $[M+H]^+$.

General Procedure for Intermediate A-59



Intermediate A-59

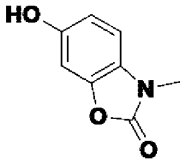
Step 1: 6-methoxy-3-methyl-2,3-dihydro-1,3-benzoxazol-2-one



[0756] To a solution of 6-methoxy-2,3-dihydro-1,3-benzoxazol-2-one (1.80 g, 10.9 mmol) and K_2CO_3 (3.01 g, 21.8 mmol) in DMF (18 mL) was added MeI (1.36 mL, 21.8 mmol). The mixture was stirred at room temperature for 1 h and was then quenched H_2O (15 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by

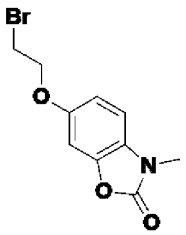
normal phase silica gel chromatography (Biotage 10 g cartridge, 0–20% EtOAc:petroleum ether) to give 6-methoxy-3-methyl-2,3-dihydro-1,3-benzoxazol-2-one. MS = 180.0 $[M+H]^+$.

Step 2: 6-hydroxy-3-methyl-2,3-dihydro-1,3-benzoxazol-2-one



[0757] To a –20 °C solution of 6-methoxy-3-methyl-2,3-dihydro-1,3-benzoxazol-2-one (1.50 g, 8.37 mmol) in DCM (3 mL) was added BBr_3 (2.42 mL, 25.1 mmol) dropwise. The mixture was warmed to 0 °C and stirred for 1 h, then poured into H_2O (15 mL). The resulting solids were isolated by filtration. The filter cake was washed with H_2O and then dried in vacuo to provide the first fraction of desired product. The filtrate was extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was washed with MeCN (2 mL), isolated by filtration, and the filter cake was dried in vacuo to give the second fraction of 6-hydroxy-3-methyl-2,3-dihydro-1,3-benzoxazol-2-one, which was combined with the first fraction and used in the subsequent step without further purification. MS = 166.3 $[M+H]^+$.

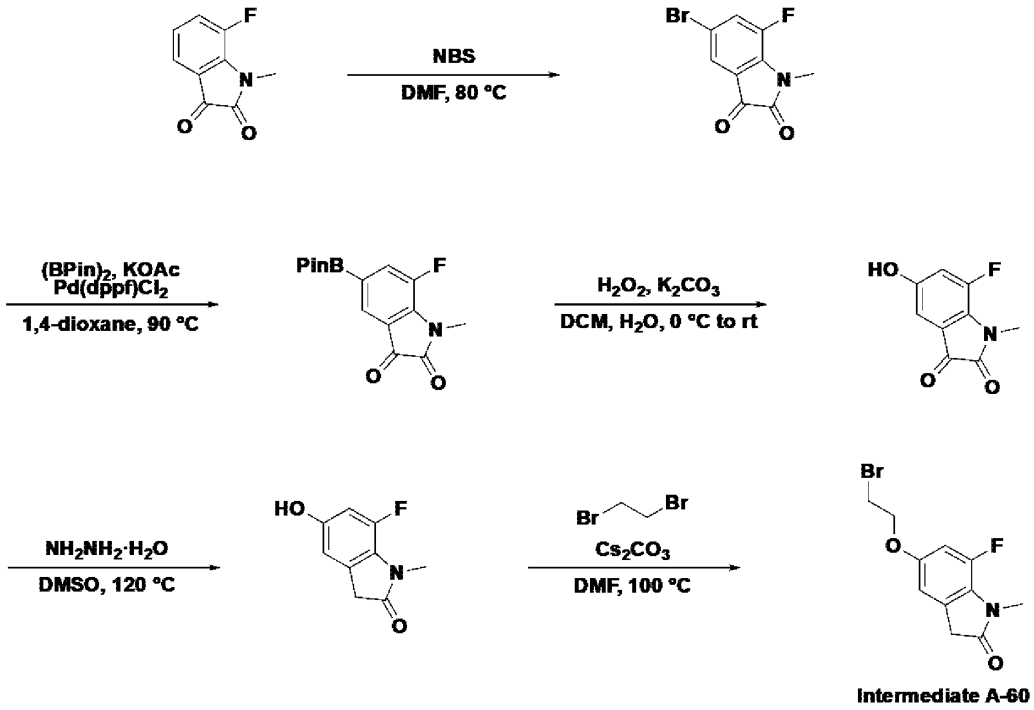
Step 3: 6-(2-bromoethoxy)-3-methyl-2,3-dihydro-1,3-benzoxazol-2-one



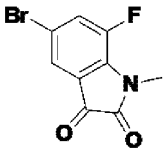
[0758] A solution of 1,2-dibromoethane (2.97 mL, 39.4 mmol), 6-hydroxy-3-methyl-2,3-dihydro-1,3-benzoxazol-2-one (1.30 g, 7.87 mmol) and Cs_2CO_3 (3.85 g, 11.8 mmol) in DMF (2 mL) was stirred at 100 °C for 16 h. After cooling to room temperature, the mixture was quenched with H_2O (15 mL). The mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 0–

30% EtOAc:petroleum ether) to give 6-(2-bromoethoxy)-3-methyl-2,3-dihydro-1,3-benzoxazol-2-one (**Intermediate A-59**). MS = 271.9 / 273.8 $[M+H]^+$.

General Procedure for Intermediate A-60

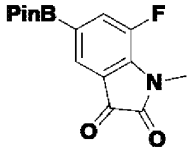


Step 1: 5-bromo-7-fluoro-1-methyl-2,3-dihydro-1H-indole-2,3-dione



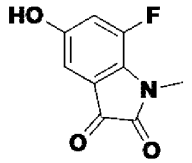
[0759] A solution of 7-fluoro-1-methyl-2,3-dihydro-1H-indole-2,3-dione (4.00 g, 22.3 mmol) and NBS (5.17 g, 29.0 mmol) in DMF (45 mL) was stirred at 80 °C for 2 h under N_2. After cooling to room temperature, the reaction mixture was poured into H_2O (100 mL) and a solid crashed out of solution. The solid was isolated via filtration and dried in vacuo to give 5-bromo-7-fluoro-1-methyl-2,3-dihydro-1H-indole-2,3-dione, which was used in the subsequent step without further purification. MS = 258.0 / 260.0 $[M+H]^+$.

Step 2: 7-fluoro-1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-indole-2,3-dione



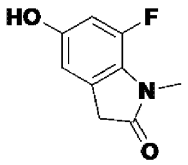
[0760] To a solution of 5-bromo-7-fluoro-1-methyl-2,3-dihydro-1H-indole-2,3-dione (3.98 g, 15.4 mmol) and bis(pinacolato)diboron (5.88 g, 23.1 mmol) in 1,4-dioxane (40 mL) was added KOAc (3.03 g, 30.9 mmol) and $Pd(dppf)Cl_2$ (1.13 g, 1.54 mmol). The mixture was stirred at 90 °C for 15 h under an atmosphere of N_2. After cooling to room temperature, the mixture was diluted with H_2O (50 mL). The mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 80 g cartridge, 0–15% EtOAc:petroleum ether) to give 7-fluoro-1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-indole-2,3-dione. MS = 306.1 $[M+H]^+$.

Step 3: 7-fluoro-5-hydroxy-1-methyl-2,3-dihydro-1H-indole-2,3-dione



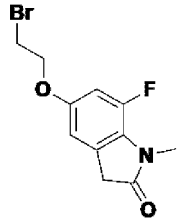
[0761] To a solution of 7-fluoro-1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-indole-2,3-dione (2.80 g, 9.18 mmol) in DCM (35 mL) were added K_2CO_3 (2.54 g, 18.4 mmol) and H_2O_2 in H_2O (2.20 mL, 30 wt%, 22.94 mmol). The mixture was stirred at room temperature for 1 h. The reaction mixture was cooled to 0 °C, quenched with saturated Na_2SO_3 (10 mL), and extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 4 g cartridge, 0–35% EtOAc:petroleum ether) to give 7-fluoro-5-hydroxy-1-methyl-2,3-dihydro-1H-indole-2,3-dione. MS = 196.1 $[M+H]^+$.

Step 4: 7-fluoro-5-hydroxy-1-methyl-2,3-dihydro-1H-indol-2-one



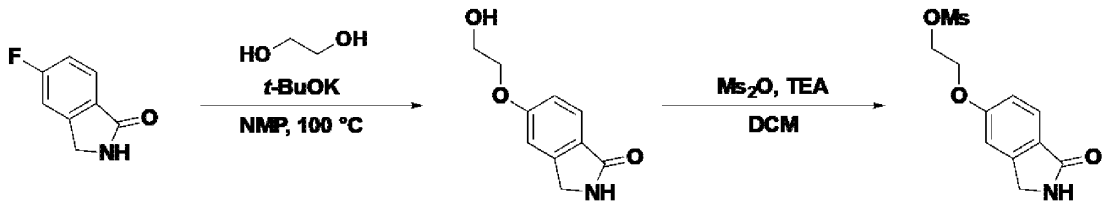
[0762] To a solution of 7-fluoro-5-hydroxy-1-methyl-2,3-dihydro-1H-indole-2,3-dione (600 mg, 3.07 mmol) in DMSO (2.5 mL) was added NH_2NH_2. H_2O (2.46 mL, 85% purity, 43.0 mmol). The mixture was stirred at 120 °C for 3 h. After cooling to 0 °C, the reaction mixture was quenched with H_2O (8 mL) and extracted with EtOAc (3 x 7 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–29% EtOAc:petroleum ether) to give 7-fluoro-5-hydroxy-1-methyl-2,3-dihydro-1H-indol-2-one. MS = 180.1 $[M–H]^-$.

Step 5: 5-(2-bromoethoxy)-7-fluoro-1-methyl-2,3-dihydro-1H-indol-2-one



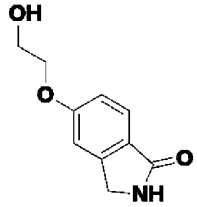
[0763] A solution of 7-fluoro-5-hydroxy-1-methyl-2,3-dihydro-1H-indol-2-one (250 mg, 1.38 mmol) and Cs_2CO_3 (1.12 g, 3.45 mmol) in 1,2-dibromoethane (6.00 mL, 79.5 mmol) was stirred at 100 °C for 15 h. After cooling to room temperature, the reaction mixture was quenched with H_2O (18 mL) and extracted with EtOAc (3 x 12 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 4 g cartridge, 0–17% EtOAc:petroleum ether) to give 5-(2-bromoethoxy)-7-fluoro-1-methyl-2,3-dihydro-1H-indol-2-one (**Intermediate A-60**). MS = 287.9 / 289.9 $[M+H]^+$.

General Procedure for Intermediate A-61



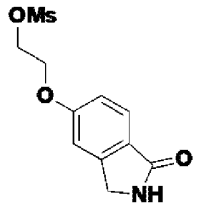
Intermediate A-61

Step 1: 5-(2-hydroxyethoxy)-2,3-dihydro-1H-isoindol-1-one



[0764] To a mixture of 5-fluoro-2,3-dihydro-1H-isoindol-1-one (750 mg, 4.96 mmol) and ethylene glycol (4.00 mL, 71.53 mmol) in NMP (4 mL) was added t-BuOK (1.67 g, 14.8 mmol). The mixture was stirred at 100 °C for 15 h. After cooling to room temperature, the reaction mixture was diluted with NMP (2 mL), and solids were removed by filtration. The filtrate was concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters Xbridge BEH C_{18} column, 1–30% MeCN:10 mM NH_4HCO_3 in H_2O) to give 5-(2-hydroxyethoxy)-2,3-dihydro-1H-isoindol-1-one. MS = 194.2 $[M+H]^+$.

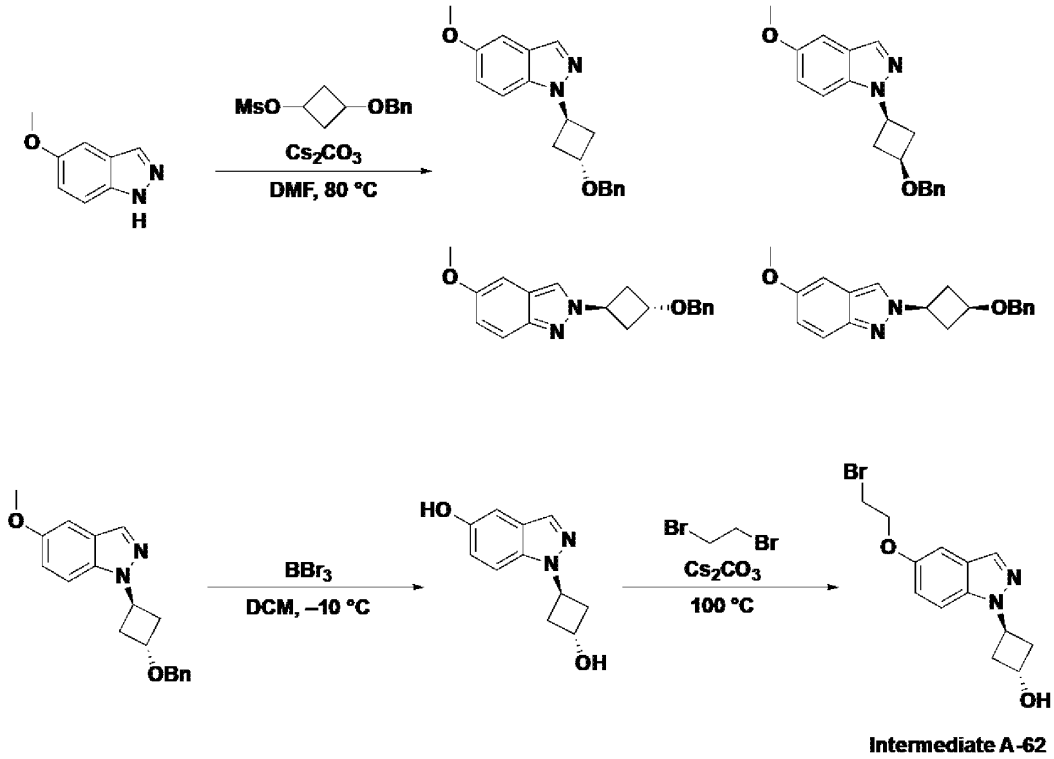
Step 2: 2-[(1-oxo-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl methanesulfonate



[0765] To a 0 °C mixture of 5-(2-hydroxyethoxy)-2,3-dihydro-1H-isoindol-1-one (100 mg, 0.518 mmol) and TEA (0.144 mL, 1.04 mmol) in DCM (2 mL) was added methanesulfonic anhydride (451 mg, 2.59 mmol) portionwise. The reaction mixture was warmed to room temperature and stirred for 15 h. The reaction mixture was then quenched with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give 2-[(1-oxo-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl methanesulfonate

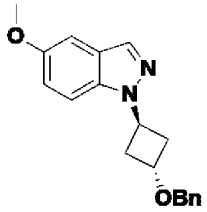
(**Intermediate A-61**), which was used in the subsequent step without further purification. MS = 272.1 $[M+H]^+$.

General Procedure for Intermediate A-62



Intermediate A-62

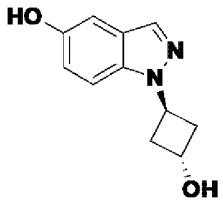
Step 1: 5-methoxy-1-[trans-3-(benzyloxy)cyclobutyl]-1H-indazole



[0766] To a mixture of 5-methoxy-1H-indazole (665 mg, 4.49 mmol) and (3-benzyloxycyclobutyl) methanesulfonate (1.15 g, 4.49 mmol) in DMF (15 mL) was added Cs_2CO_3 (2.92 g, 8.98 mmol). The mixture was stirred at 80 °C for 15 h. After cooling to room temperature, the reaction mixture was quenched with H_2O (45 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude

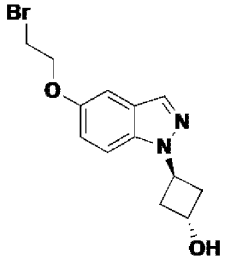
residue was purified by normal phase silica gel chromatography (Biotage 80 g cartridge, 0–50% EtOAc:petroleum ether). The first eluting product, desired 5-methoxy-1-[*trans*-3-(benzyloxy)cyclobutyl]-1H-indazole: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.40–7.35 (m, 6H), 7.08–7.04 (m, 2H), 4.67–4.59 (m, 1H), 4.53 (s, 2H), 4.06–4.00 (m, 1H), 3.86 (s, 3H), 2.93–2.83 (m, 4H). MS = 309.3 $[M+H]^+$. The second eluting product, desired 5-methoxy-1-[*cis*-3-(benzyloxy)cyclobutyl]-1H-indazole: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.41–7.29 (m, 6H), 7.07–7.04 (m, 2H), 5.29–5.22 (m, 1H), 4.54–4.50 (m, 3H), 3.86 (s, 3H), 2.96–2.92 (m, 2H), 2.73–2.67 (m, 2H). The third eluting product, undesired 5-methoxy-2-[(*trans*)-3-(benzyloxy)cyclobutyl]-2H-indazole: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.64 (d, J = 9.6 Hz, 1H), 7.39–7.37 (m, 5H), 7.00 (dd, J = 9.6, 2.4 Hz, 1H), 6.87 (d, J = 2.4 Hz, 1H), 5.21–5.17 (m, 1H), 4.56–4.52 (m, 1H), 4.51 (s, 2H), 3.84 (s, 3H), 2.99–2.92 (m, 2H), 2.77–2.72 (m, 2H). The fourth eluting product, undesired 5-methoxy-2-[(*cis*)-3-(benzyloxy)cyclobutyl]-2H-indazole: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.62 (d, J = 9.2 Hz, 1H), 7.38–7.33 (m, 5H), 7.99 (dd, J = 9.2, 2.4 Hz, 1H), 6.87 (d, J = 2.4 Hz, 1H), 4.67–4.62 (m, 1H), 4.52 (s, 2H), 4.06–3.99 (m, 1H), 3.84 (s, 3H), 3.01–2.98 (m, 2H), 2.70–2.67 (m, 2H).

Step 2: 1-[*trans*-3-hydroxycyclobutyl]-1H-indazol-5-ol



[0767] To a –10 °C solution of 5-methoxy-1-[trans-3-(benzyloxy)cyclobutyl]-1H-indazole (250 mg, 0.811 mmol) in DCM (2.5 mL) was added BBr_3 (156 µL, 1.62 mmol). The mixture was stirred at –10 °C for 4 h, and then quenched with MeOH (10 mL). The solution was placed in a 0 °C ice bath and adjusted to pH = 7–8 with the dropwise addition of saturated aqueous $NaHCO_3$. The biphasic mixture was concentrated in vacuo, and the remaining aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 40 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–100% EtOAc:petroleum ether) to give 1-[*trans*-3-hydroxycyclobutyl]-1H-indazol-5-ol. MS = 205.2 $[M+H]^+$.

Step 3: *trans*-3-[5-(2-bromoethoxy)-1H-indazol-1-yl]cyclobutan-1-ol

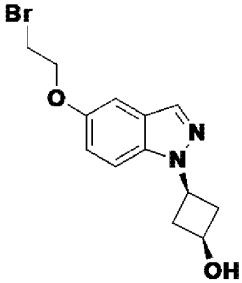


[0768] To a solution of 1-[trans-3-hydroxycyclobutyl]-1H-indazol-5-ol (100 mg, 0.490 mmol) in 1,2-dibromoethane (10 mL, 133 mmol) was added Cs_2CO_3 (479 mg, 1.47 mmol). The mixture was stirred at 100 °C for 15 h. After cooling to room temperature, the reaction mixture was quenched with H_2O (30 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 25 g cartridge, 0–100% EtOAc:petroleum ether) to give *trans*-3-[5-(2-bromoethoxy)-1H-indazol-1-yl]cyclobutan-1-ol **(Intermediate A-62)**. MS = 311.2 / 313.2 $[M+H]^+$.

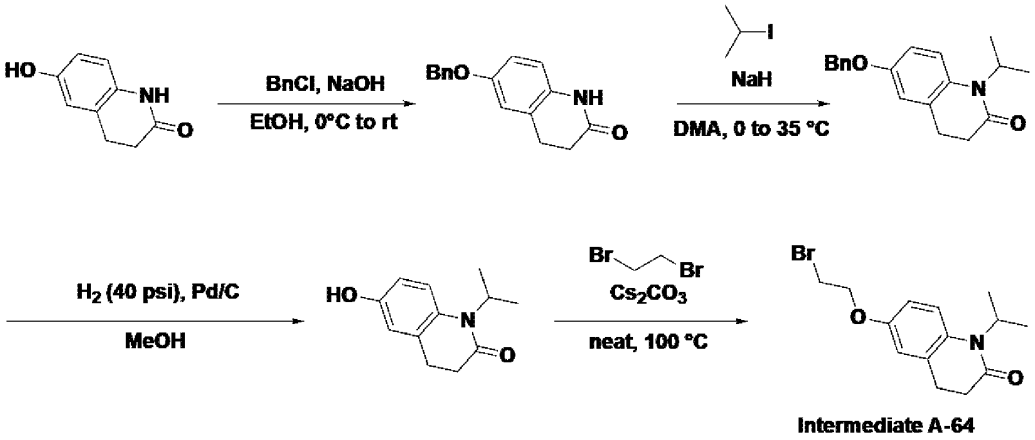
[0769] The following intermediate in Table 10 was prepared using procedures similar to those described for **Intermediate A-62**, using the appropriate starting materials.

General Procedures for Intermediate A-63

Table 10.

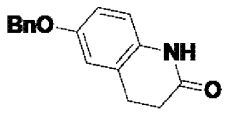
Intermediate #	Structure	Name	Exact Mass $[M+H]^+$
A-63		*cis*-3-[5-(2-bromoethoxy)-1H-indazol-1-yl]cyclobutan-1-ol	Calc'd 311.0 / 313.0 Found 311.2 / 313.2

General Procedure for Intermediate A-64



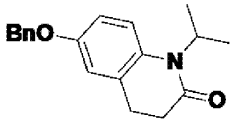
Intermediate A-64

Step 1: 6-(benzyloxy)-1,2,3,4-tetrahydroquinolin-2-one



[0770] To a 0 °C solution of 6-hydroxy-1,2,3,4-tetrahydroquinolin-2-one (1.00 g, 6.13 mmol) in EtOH (10 mL) were added NaOH (490 mg, 12.3 mmol) and benzyl chloride (2.12 mL, 18.4 mmol). The mixture was stirred at room temperature for 15 h, was then poured into H_2O (20 mL), and filtered to give a filter cake. The filter cake was washed with EtOH, triturated with MTBE, then dried in vacuo to give 6-(benzyloxy)-1,2,3,4-tetrahydroquinolin-2-one, which was taken to the next step without further purification. MS = 254.2 $[M+H]^+$.

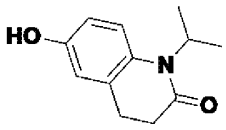
Step 2: 6-(benzyloxy)-1-(propan-2-yl)-1,2,3,4-tetrahydroquinolin-2-one



[0771] To a 0 °C solution of 6-(benzyloxy)-1,2,3,4-tetrahydroquinolin-2-one (1.50 g, 5.92 mmol) in DMA (20 mL) under N_2 atmosphere was added NaH (616 mg, 60 wt% in mineral oil, 15.4 mmol). After 30 min, 2-iodopropane (2.37 mL, 23.7 mmol) was added. The reaction mixture was warmed to room temperature, and then heated to 35 °C and stirred for 15.5 h under an atmosphere of N_2. After cooling to 0 °C, the reaction mixture was quenched with H_2O (30 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica

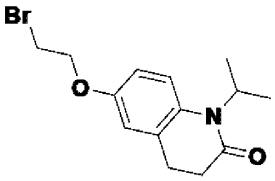
gel chromatography (Biotage 20 g cartridge, 0–27% EtOAc:petroleum ether) to give 6-(benzyloxy)-1-(propan-2-yl)-1,2,3,4-tetrahydroquinolin-2-one. MS = 296.1 $[M+H]^+$.

Step 3: 6-hydroxy-1-(propan-2-yl)-1,2,3,4-tetrahydroquinolin-2-one



[0772] To a solution of 6-(benzyloxy)-1-(propan-2-yl)-1,2,3,4-tetrahydroquinolin-2-one (1.30 g, 4.40 mmol) in MeOH (25 mL) was added Pd/C (0.30 g, 10 wt%, 0.28 mmol). The mixture was stirred at 40 °C for 16 h under an atmosphere of H_2 (40 psi). After cooling to room temperature, the reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo to give 6-hydroxy-1-(propan-2-yl)-1,2,3,4-tetrahydroquinolin-2-one, which was used in the subsequent step without further purification. MS = 206.0 $[M+H]^+$.

Step 4: 6-(2-bromoethoxy)-1-(propan-2-yl)-1,2,3,4-tetrahydroquinolin-2-one

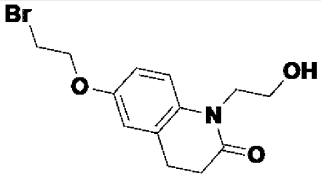
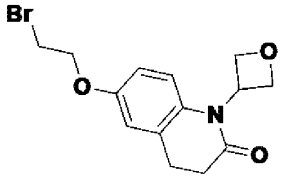
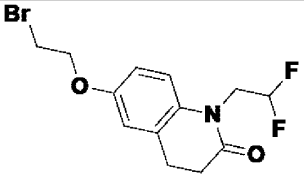
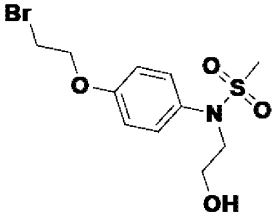


[0773] To a solution of 6-hydroxy-1-(propan-2-yl)-1,2,3,4-tetrahydroquinolin-2-one (810 mg, 3.95 mmol) in 1,2-dibromoethane (12 mL, 159 mmol) was added Cs_2CO_3 (2.57 g, 7.89 mmol). The mixture was stirred at 100 °C for 15 h. After cooling to room temperature, the reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 25 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–20% EtOAc:petroleum ether) to give 6-(2-bromoethoxy)-1-(propan-2-yl)-1,2,3,4-tetrahydroquinolin-2-one **(Intermediate A-64)**. MS = 312.0 / 314.0 $[M+H]^+$.

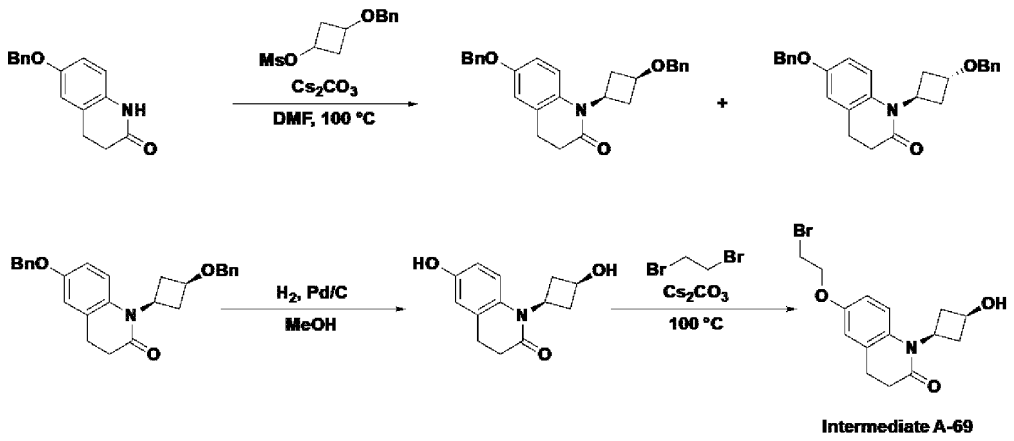
[0774] The following intermediates in Table 11 were prepared according to procedures similar those described for **Intermediate A-64** using the appropriate starting materials.

General Procedure for Intermediates A-65 to A-68

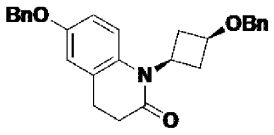
Table 11.

Intermediate #	Structure	Name	Exact Mass $[M+H]^+$
A-65		6-(2-bromoethoxy)-1-(2-hydroxyethyl)-1,2,3,4-tetrahydroquinolin-2-one	Calc'd 314.0 / 316.0 Found 313.9 / 315.9
A-66		6-(2-bromoethoxy)-1-(oxetan-3-yl)-1,2,3,4-tetrahydroquinolin-2-one	Calc'd 326.0 / 328.0 Found 326.1 / 328.1
A-67		6-(2-bromoethoxy)-1-(2,2-difluoroethyl)-1,2,3,4-tetrahydroquinolin-2-one	Calc'd 334.0 / 336.0 Found 334.1 / 336.1
A-68		*N*-[4-(2-bromoethoxy)phenyl]-*N*-(2-hydroxyethyl)methanesulfonamide	Calc'd 338.0 / 340.0 Found 338.1 / 340.1

General Procedure for Intermediate A-69

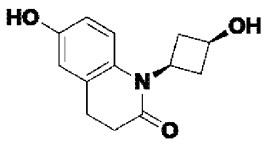


Step 1: 6-(benzyloxy)-1-[(*cis*)-3-(benzyloxy)cyclobutyl]-1,2,3,4-tetrahydroquinolin-2-one



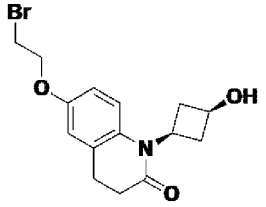
[0775] To a solution of 6-(benzyloxy)-1,2,3,4-tetrahydroquinolin-2-one (300 mg, 1.18 mmol) in DMF (4 mL) was added Cs_2CO_3 (1.54 g, 4.74 mmol) and 3-(benzyloxy)cyclobutyl methanesulfonate (910 mg, 3.55 mmol). The mixture was stirred at 100 °C for 12 h. After cooling to room temperature, the reaction mixture was poured into H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), filtered, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 0–15% EtOAc:petroleum ether). The first eluting isomer, minor product 6-(benzyloxy)-1-[(*trans*)-3-(benzyloxy)cyclobutyl]-1,2,3,4-tetrahydroquinolin-2-one: ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.44–7.33 (m, 10H), 6.93 (d, J = 2.4 Hz, 1H), 6.92–6.80 (m, 2H), 5.05 (s, 2H), 4.62–4.56 (m, 1H), 4.40 (s, 2H), 4.14–4.11 (m, 1H), 2.76–3.73 (m, 2H), 2.53–2.50 (m, 2H), 2.44–2.37 (m, 4H). The second eluting isomer, desired major product 6-(benzyloxy)-1-[(*cis*)-3-(benzyloxy)cyclobutyl]-1,2,3,4-tetrahydroquinolin-2-one: ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.45–7.39 (m, 4H), 7.33–7.28 (m, 6H), 6.94 (d, J = 2.4 Hz, 1H), 6.93–6.77 (m, 2H), 5.06 (s, 2H), 4.36 (s, 2H), 3.93–3.88 (m, 1H), 3.80–3.77 (m, 1H), 2.88–2.86 (m, 2H), 2.77–2.73 (m, 2H), 2.40–2.37 (m, 2H), 1.95–1.89 (m, 2H).

Step 2: 6-hydroxy-1-[(*cis*)-3-hydroxycyclobutyl]-1,2,3,4-tetrahydroquinolin-2-one



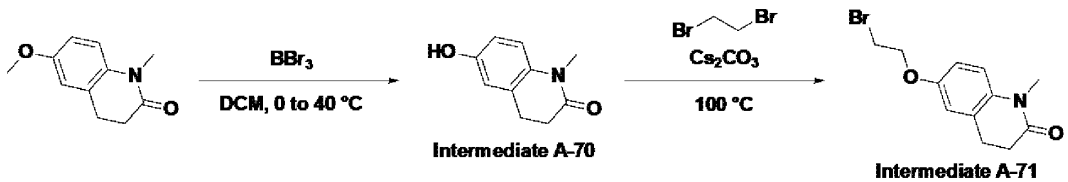
[0776] To a solution of 6-(benzyloxy)-1-[(*cis*)-3-(benzyloxy)cyclobutyl]-1,2,3,4-tetrahydroquinolin-2-one (400 mg, 0.967 mmol) in MeOH (20 mL) under N_2 atmosphere was added Pd/C (50 mg, 10 wt%, 0.47 mmol) The mixture was degassed and purged with H_2 (3x), then stirred under H_2 (50 Psi) atmosphere at room temperature for 12 h. The reaction mixture was filtered through Celeit and concentrated under in vacuo to give 6-hydroxy-1-[(*cis*)-3-hydroxycyclobutyl]-1,2,3,4-tetrahydroquinolin-2-one, which was used in the subsequent step without further purification. MS = 234.3 $[M+H]^+$.

Step 3: 6-(2-bromoethoxy)-1-[(*cis*)-3-hydroxycyclobutyl]-1,2,3,4-tetrahydroquinolin-2-one

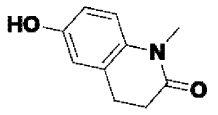


[0777] To a solution of 6-hydroxy-1-[(*cis*)-3-hydroxycyclobutyl]-1,2,3,4-tetrahydroquinolin-2-one (200 mg, 0.857 mmol) in 1,2-dibromoethane (5 mL, 133 mmol) was added Cs_2CO_3 (558 mg, 1.71 mmol). The mixture was stirred at 100 °C for 12 h. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo. The residue was diluted with H_2O (10 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Isco 4 g cartridge, 0–47% EtOAc:petroleum ether) to give 6-(2-bromoethoxy)-1-[(*cis*)-3-hydroxycyclobutyl]-1,2,3,4-tetrahydroquinolin-2-one (**Intermediate A-69**). MS = 340.1 / 342.1 $[M+H]^+$.

General Procedure for Intermediates A-70 & A-71

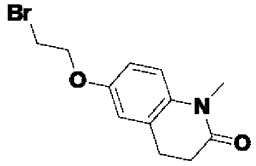


Step 1: 6-hydroxy-1-methyl-1,2,3,4-tetrahydroquinolin-2-one



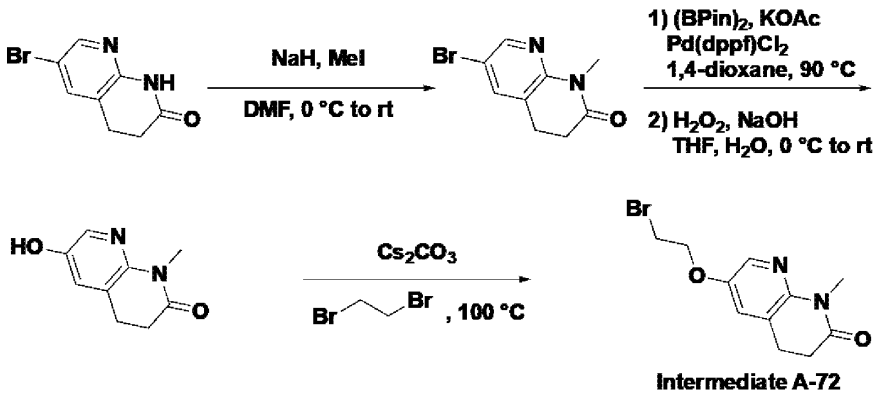
[0778] To a 0 °C solution of 6-methoxy-1-methyl-1,2,3,4-tetrahydroquinolin-2-one (150 mg, 0.784 mmol) in DCM (5 mL) was added BBr_3 (378 µL, 3.92 mmol) dropwise. The mixture was stirred at 40 °C for 4 h. After cooling to 0 °C, the reaction mixture was quenched with H_2O (10 mL) and adjusted to pH = 8 with saturated aqueous Na_2CO_3. The biphasic mixture was extracted with EtOAc (5 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 80–100% EtOAc:petroleum ether) to give 6-hydroxy-1-methyl-1,2,3,4-tetrahydroquinolin-2-one (**Intermediate A-70**). MS = 178.1 $[M+H]^+$.

Step 2: 6-(2-bromoethoxy)-1-methyl-1,2,3,4-tetrahydroquinolin-2-one

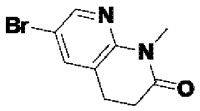


[0779] To a solution of 6-hydroxy-1-methyl-3,4-dihydroquinolin-2-one (0.300 g, 1.69 mmol) in 1,2-dibromoethane (5.11 mL, 67.7 mmol) was added Cs_2CO_3 (1.10 g, 3.39 mmol). The mixture was stirred at 100 °C for 4 h. After cooling to 0 °C, the reaction mixture was quenched with H_2O (20 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 4 g cartridge, 0–25% EtOAc:petroleum ether) to give 6-(2-bromoethoxy)-1-methyl-1,2,3,4-tetrahydroquinolin-2-one (**Intermediate A-71**). MS = 284.0 / 286.1 $[M+H]^+$.

General Procedure for Intermediate A-72

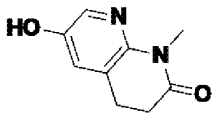


Step 1: 6-bromo-1-methyl-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



[0780] To a 0 °C solution of 6-bromo-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (739 mg, 3.26 mmol) in DMF (11 mL) was added NaH (156 mg, 60 wt%, 3.91 mmol). The mixture was stirred at for 1 h and then MeI (693 mg, 4.88 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was then quenched with H_2O (30 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 25 g cartridge, 0–100% EtOAc:Hexanes) to give 6-bromo-1-methyl-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.31 (d, J = 2.3 Hz, 1H), 7.59 (dd, J = 2.3, 1.1 Hz, 1H), 3.45 (s, 3H), 2.91 (t, J = 7.5 Hz, 2H), 2.72 (t, J = 7.5 Hz, 2H).

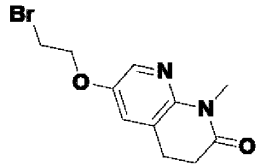
Step 2: 6-hydroxy-1-methyl-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



[0781] A solution of 6-bromo-1-methyl-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (450 mg, 1.87 mmol), potassium acetate (366 mg, 3.73 mmol), bis(pinacolato)diboron (569 mg 2.24 mmol) in 1,4-dioxane (9.3 mL) was sparged with nitrogen for 10 min. $Pd(dppf)Cl_2$ (68 mg, 0.093 mmol) was then added, and the reaction was heated to 90 °C for 2 h. The reaction mixture was cooled to room

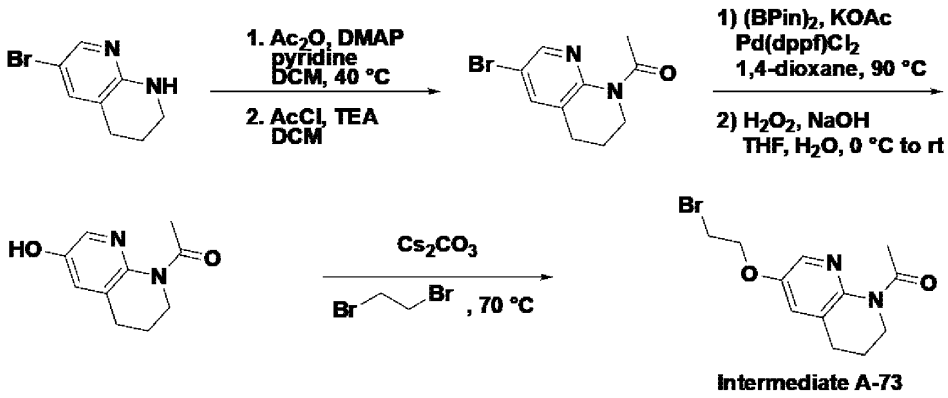
temperature, filtered over Celite, and washed with EtOAc (30 mL). The filtrate was concentrated in vacuo. The crude residue was purified by normal phase chromatography (Biotage 25 g cartridge, 10% EtOAc:hexanes). The resulting residue was dissolved in THF (25 mL) and H_2O (10 mL), and 1 M aqueous NaOH (5 mL) was added. The solution was cooled to 0 °C and H_2O_2 in H_2O (423 mg, 30 wt%, 3.7 mmol) was added dropwise over 3 min. The reaction mixture was allowed to warm room temperature and stirred for 16 h. The mixture was adjusted to pH = 5 with 1.0 M aqueous HCl. The reaction mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 25 g cartridge, 10% MeOH:DCM) to give 6-hydroxy-1-methyl-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.57 (s, 1H), 7.77 (d, J = 2.7 Hz, 1H), 7.09 (d, J = 2.8 Hz, 1H), 3.26 (s, 3H), 2.81 (t, J = 7.5 Hz, 2H), 2.62–2.36 (m, 2H). MS = 179.1 $[M+H]^+$.

Step 3: 6-(2-bromoethoxy)-1-methyl-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one

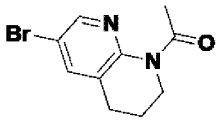


[0782] To a solution of 6-hydroxy-1-methyl-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (221 mg, 1.24 mmol) in 1,2-dibromoethane (4.1 mL, 53 mmol) was added Cs_2CO_3 (1.2 g, 3.7 mmol) and the reaction was stirred at 100 °C for 6 h. The reaction was cooled to room temperature and diluted with EtOAc (10 mL). The reaction mixture was filtered over Celite and washed with EtOAc (30 mL). The reaction mixture was then concentrated in vacuo to afford 6-(2-bromoethoxy)-1-methyl-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (**Intermediate A-72**) which was used in the subsequent step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, J = 2.8 Hz, 1H), 7.11 (d, J = 2.8 Hz, 1H), 4.33 (t, J = 6.1 Hz, 2H), 3.65 (t, J = 6.1 Hz, 2H), 3.45 (s, 3H), 2.88 (t, J = 7.6 Hz, 2H), 2.69 (t, J = 7.6 Hz, 2H).

General Procedure for Intermediate A-73

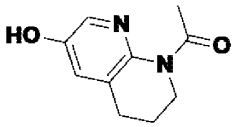


Step 1: 1-(6-bromo-1,2,3,4-tetrahydro-1,8-naphthyridin-1-yl)ethan-1-one



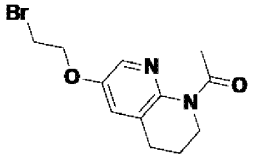
[0783] To a solution of 6-bromo-1,2,3,4-tetrahydro-1,8-naphthyridine (500 mg, 2.35 mmol) in DCM (12 mL) was added pyridine (757 µL, 9.39 mmol), acetic anhydride (660 µL, 7.05 mmol) and DMAP (5.0 mg, 0.041 mmol). The mixture was heated to 40 °C and stirred at for 16 h, and then cooled to room temperature. The reaction mixture was then quenched with H_2O (30 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 25 g cartridge, 0–100% EtOAc:Hexanes) to give a mixture of 1-(6-bromo-1,2,3,4-tetrahydro-1,8-naphthyridin-1-yl)ethan-1-one and unreacted 6-bromo-1,2,3,4-tetrahydro-1,8-naphthyridine. The mixture was redissolved in DCM (11.7 mL) and TEA (326 µL, 2.35 mmol) was added followed by acetyl chloride (167 µL, 2.35 mmol). After stirring for 16 h, the reaction mixture was quenched with H_2O (30 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 25 g cartridge, 0–100% EtOAc:Hexanes) to afford 1-(6-bromo-1,2,3,4-tetrahydro-1,8-naphthyridin-1-yl)ethan-1-one.

Step 2: 1-(6-hydroxy-1,2,3,4-tetrahydro-1,8-naphthyridin-1-yl)ethan-1-one



[0784] A solution of 1-(6-bromo-1,2,3,4-tetrahydro-1,8-naphthyridin-1-yl)ethan-1-one (435 mg, 1.71 mmol), potassium acetate (335 mg, 3.41 mmol), and bis(pinacolato)diboron (520 mg 2.05 mmol) in 1,4-dioxane (8.5 mL) was sparged with N_2 for 10 min. $Pd(dppf)Cl_2$ (62 mg, 0.085 mmol) was added, and the reaction was heated at 90 °C for 2 h. The reaction mixture was cooled to room temperature, filtered over Celite and washed with EtOAc (30 mL), then concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 25 g cartridge, 10% EtOAc:Hexanes). The resulting residue was dissolved in THF (25 mL) and H_2O (10 mL), and 1.0 M aqueous NaOH (5 mL) was added. The solution was cooled to 0 °C and H_2O_2 in H_2O (387 mg, 30 wt%, 3.4 mmol) was added dropwise over 3 min. The reaction mixture was allowed to warm room temperature and stirred for 16 h. The mixture was adjusted to pH = 5 with 1.0 M aqueous HCl. The reaction mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase chromatography (Biotage 25 g cartridge, 10% MeOH:DCM) to give 1-(6-hydroxy-1,2,3,4-tetrahydro-1,8-naphthyridin-1-yl)ethan-1-one. ^1H NMR (500 MHz, $CDCl_3$, 11/12 H): δ 7.92 (d, J = 2.8 Hz, 1H), 7.04 (d, J = 2.8 Hz, 1H), 3.89 (t, J = 6.3 Hz, 2H), 2.75 (t, J = 6.6 Hz, 2H), 2.41 (s, 3H), 2.00–1.85 (m, 2H). MS = 193.1 $[M+H]^+$.

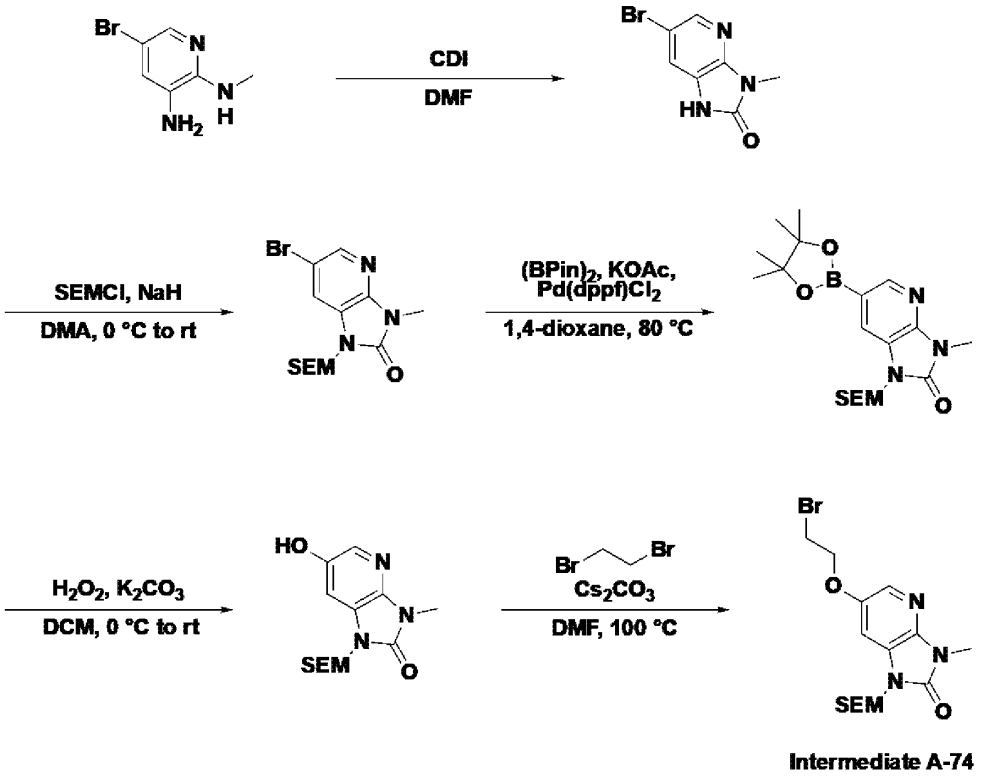
Step 3: 1-[6-(2-bromoethoxy)-1,2,3,4-tetrahydro-1,8-naphthyridin-1-yl]ethan-1-one



[0785] To a solution of 1-(6-hydroxy-1,2,3,4-tetrahydro-1,8-naphthyridin-1-yl)ethan-1-one (124 mg, 0.645 mmol) in 1,2-dibromoethane (2.1 mL, 27.8 mmol) was added Cs_2CO_3 (631 mg, 1.94 mmol), and the reaction was stirred at 70 °C for 6 h. The reaction was cooled to room temperature and diluted with EtOAc (10 mL). The reaction mixture was filtered over Celite and washed with EtOAc (30 mL). The reaction mixture was then concentrated in vacuo to afford 1-[6-(2-bromoethoxy)-1,2,3,4-tetrahydro-1,8-naphthyridin-1-yl]ethan-1-one (**Intermediate A-73**) which

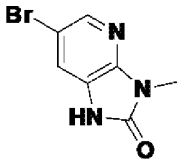
was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, J = 2.9 Hz, 1H), 7.08 (d, J = 2.9 Hz, 1H), 4.35 (t, J = 6.1 Hz, 2H), 3.90 (t, J = 6.2 Hz, 2H), 3.67 (t, J = 6.1 Hz, 2H), 2.78 (t, J = 6.7 Hz, 2H), 2.43 (s, 3H), 1.98–1.93 (m, 2H).

General Procedure for Intermediate A-74



Intermediate A-74

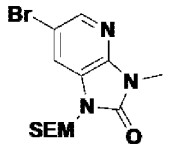
Step 1: 6-bromo-3-methyl-1H,2H,3H-imidazo[4,5-b]pyridin-2-one



[0786] To a solution of 5-bromo-*N*2-methylpyridine-2,3-diamine (1.00 g, 4.95 mmol) in DMF (15 mL) was added CDI (3.21 g, 19.8 mmol). The mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography

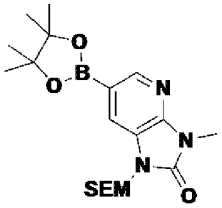
(Biotage 20 g cartridge, 0–100% EtOAc:Hexanes) to give 6-bromo-3-methyl-1H,2H,3H-imidazo[4,5-b]pyridin-2-one. MS = 228.1 / 230.1 $[M+H]^+$.

Step 2: 6-bromo-3-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H,2H,3H-imidazo[4,5-b]pyridin-2-one



[0787] To a 0 °C solution of 6-bromo-3-methyl-1H,2H,3H-imidazo[4,5-b]pyridin-2-one (500 mg, 2.19 mmol) in DMA (8 mL) was added NaH (263 mg, 60 wt% in mineral oil, 6.58 mmol) portionwise. The mixture was stirred at 0 °C for 30 min and then 2-(trimethylsilyl)ethoxymethyl chloride (0.582 mL, 3.29 mmol) was added dropwise. The mixture was allowed to warm to room temperature and was stirred for an additional 4.5 h. The reaction mixture was cooled to 0 °C and then quenched with saturated aqueous NH_4Cl (5 mL), diluted with H_2O (5 mL), and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 10 g cartridge, 0–100% EtOAc:Hexanes) to give 6-bromo-3-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H,2H,3H-imidazo[4,5-b]pyridin-2-one. MS = 358.1 / 360.1 $[M+H]^+$.

Step 3: 3-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H,2H,3H-imidazo[4,5-b]pyridin-2-one



[0788] A mixture of 6-bromo-3-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H,2H,3H-imidazo[4,5-b]pyridin-2-one (1.80 g, 5.02 mmol), bis(pinacolato)diboron (1.53 g, 6.03 mmol), $Pd(dppf)Cl_2$ (368 mg, 0.502 mmol), and KOAc (986 mg, 10.1 mmol) in 1,4-dioxane (25 mL) was degassed and purged with N_2 (3x). The mixture was heated at 80 °C for 12 h. After cooling to room temperature, the reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (2 x

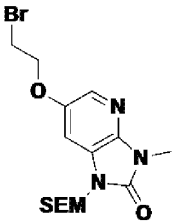
30 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 0–100% EtOAc:petroleum ether) to give 3-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H,2H,3H-imidazo[4,5-b]pyridin-2-one. MS = 406.3 $[M+H]^+$.

Step 4: 6-hydroxy-3-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H,2H,3H-imidazo[4,5-b]pyridin-2-one



[0789] To a 0 °C mixture of 3-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H,2H,3H-imidazo[4,5-b]pyridin-2-one (2.00 g, 4.93 mmol) in DCM (30 mL) was added H_2O_2 in H_2O (1.19 mL, 30 wt%, 12.3 mmol) and K_2CO_3 (1.36 g, 9.87 mmol). The mixture was stirred at room temperature for 10 h. The reaction mixture was cooled to 0 °C, quenched with saturated aqueous Na_2SO_3 (40 mL), and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with saturated aqueous Na_2SO_3 (40 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 0–100% EtOAc:petroleum ether) to give 6-hydroxy-3-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H,2H,3H-imidazo[4,5-b]pyridin-2-one. MS = 296.2 $[M+H]^+$.

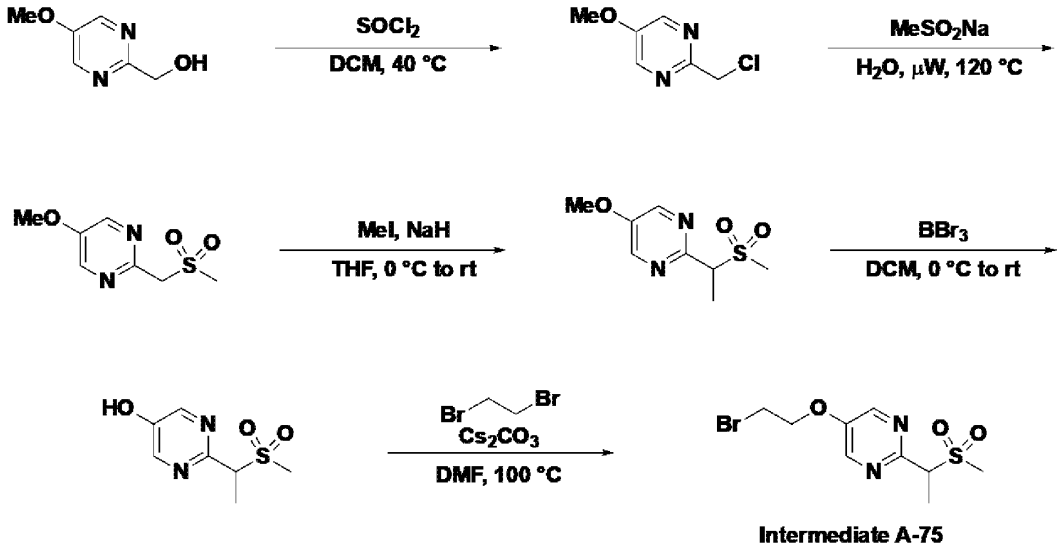
Step 5: 6-(2-bromoethoxy)-3-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H,2H,3H-imidazo[4,5-b]pyridin-2-one



[0790] To a mixture of 6-hydroxy-3-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H,2H,3H-imidazo[4,5-b]pyridin-2-one (600 mg, 2.03 mmol) and 1,2-dibromoethane (1.53 mL, 20.3 mmol) in

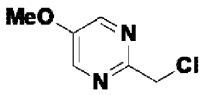
DMF (5 mL) was added Cs_2CO_3 (1.32 g, 4.06 mmol). The mixture was stirred at 100 °C for 10 h. After cooling to room temperature, the reaction mixture was quenched by the addition of H_2O (10 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 10 g cartridge, 0–100% EtOAc:petroleum ether) to give 6-(2-bromoethoxy)-3-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H,2H,3H-imidazo[4,5-b]pyridin-2-one (**Intermediate A-74**). MS = 402.2 / 404.1 $[M+H]^+$.

General Procedure for Intermediate A-75



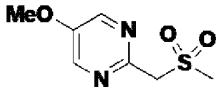
Intermediate A-75

Step 1: 2-(Chloromethyl)-5-methoxypyrimidine



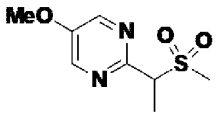
[0791] To a solution of (5-methoxypyrimidin-2-yl)methanol(4.00 g, 28.5 mmol) in DCM (143 mL) under N_2 atmosphere was added thionyl chloride (6.21 mL, 64.2 mmol). The reaction mixture was heated at 40 °C for 2 h. After cooling to room temperature, the reaction was quenched with H_2O (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo give 2-(chloromethyl)-5-methoxypyrimidine, which was used in the subsequent step without further purification.

Step 2: -(Methanesulfonylmethyl)-5-methoxypyrimidine



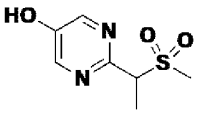
[0792] To a microwave vial equipped with a stir bar was added 2-(chloromethyl)-5-methoxypyrimidine (1.00 g, 6.31 mmol) and sodium methanesulfinate (0.837 g, 8.20 mmol) followed by H_2O (12.6 mL). The vial was sealed and heated at 120 °C in a microwave at 40 psi for 30 min. The reaction mixture was cooled to 0 °C the resulting solid was isolated by filtration and dried in vacuo to give 2-(methanesulfonylmethyl)-5-methoxypyrimidine, which was used in the subsequent step without further purification. MS = 203.0 $[M+H]^+$.

Step 3: 2-(1-Methanesulfonylethyl)-5-methoxypyrimidine



[0793] To a solution of 2-(methanesulfonylmethyl)-5-methoxypyrimidine (1.25 g, 6.18 mmol) in DMF (29.4 mL) at 0 °C was added NaH (0.494 g, 60 wt% in mineral oil, 12.4 mmol). The reaction was mixture was allowed to warm to room temperature and stirred for 10 min. MeI (0.366 mL, 5.87 mmol) was added, and the mixture was allowed to stir at room temperature for 1 h. The reaction mixture was quenched with H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were combined and washed with 5% aqueous LiCl solution (100 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by normal phase silica gel chromatography (0–100% EtOAc in Hexanes) provided 2-(1-methanesulfonylethyl)-5-methoxypyrimidine. MS = 217.12 $[M+H]^+$.

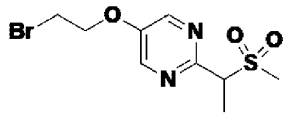
Step 4: 2-(1-Methanesulfonylethyl)pyrimidin-5-ol



[0794] To a solution of 2-(1-methanesulfonylethyl)-5-methoxypyrimidine (500 mg, 2.31 mmol) in DCM (11.6 mL) at 0 °C was added a solution of 1.0 M BBr_3 in DCM (11.6 mL, 11.6 mmol). The mixture was allowed to warm to room temperature and stirred for 5 h. The reaction mixture was concentrated in vacuo, then re-dissolved in DCM and concentrated in vacuo (2x). The residue was

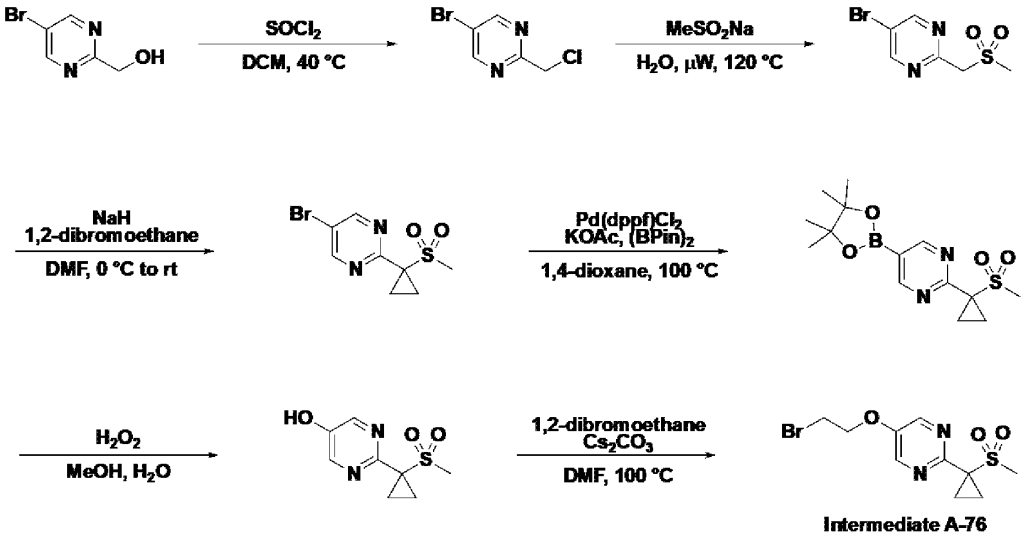
quenched with MeOH (30 mL), and then concentrated in vacuo to provide 5-(2-bromoethoxy)-2-(1-methanesulfonylethyl)pyrimidine, which was used in the subsequent step without further purification. MS = 202.95 $[M+H]^+$.

Step 5: 5-(2-Bromoethoxy)-2-(1-methanesulfonylethyl)pyrimidine



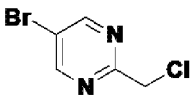
[0795] To a solution of 2-(1-methanesulfonylethyl)pyrimidin-5-ol (500 mg, 2.47 mmol) in 1,2-dibromoethane (8.24 mL, 93.9 mmol) and DMF (0.5 mL) was added Cs_2CO_3 (2.42 g, 7.42 mmol). The reaction mixture was heated at 100 °C for 6 h, then allowed to cool to room temperature. The reaction mixture was then diluted with 20 mL EtOAc, filtered over Celite and concentrated in vacuo to afford crude 5-(2-bromoethoxy)-2-(1-methanesulfonylethyl)pyrimidine (**Intermediate A-75**), which was used in the subsequent step without further purification. MS = 309.0 / 311.0 $[M+H]^+$.

General Procedure for Intermediate A-76



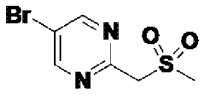
Intermediate A-76

Step 1: 5-Bromo-2-(chloromethyl)pyrimidine



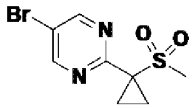
[0796] To a solution of (5-bromopyrimidin-2-yl)methanol (5.00 g, 26.5 mmol) in DCM (132 mL) under N_2 atmosphere was added thionyl chloride (5.76 mL, 79.4 mmol). The reaction mixture was heated at 40 °C for 2 h. After cooling to room temperature, the mixture was quenched with H_2O (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, then concentrated in vacuo to give 5-bromo-2-(chloromethyl)pyrimidine, which was used in the subsequent step without further purification. MS = 207.0 / 209.0 $[M+H]^+$.

Step 2: 5-Bromo-2-(methanesulfonylmethyl)pyrimidine



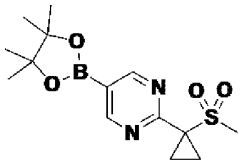
[0797] To a microwave vial equipped with a stir bar were added 5-bromo-2-(chloromethyl)pyrimidine (2.00 g, 9.64 mmol), sodium methanesulfinate (1.28 g, 12.5 mmol), and then H_2O (19 mL). The vial was sealed and heated at 120 °C in a microwave at 40 psi for 30 min. The reaction mixture was then cooled to 0 °C and the resulting solid was isolated by filtration and dried in vacuo to give 2-(methanesulfonylmethyl)-5-methoxypyrimidine, which was used in the subsequent step without further purification. MS = 251.0 / 253.0 $[M+H]^+$.

Step 3: 5-Bromo-2-(1-methanesulfonylcyclopropyl)pyrimidine



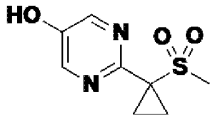
[0798] To a solution of 5-bromo-2-(methanesulfonylmethyl)pyrimidine (250 mg, 1.00 mmol) in DMF (5.0 mL) at 0 °C was added NaH (0.119 g, 60 wt% in mineral oil, 2.99 mmol). The reaction mixture was allowed to warm to room temperature for 10 min, then 1,2-dibromoethane (0.561 g, 2.99 mmol) was added. The mixture was allowed to stir for 1 h, then was diluted with H_2O (20 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with 5% aqueous LiCl solution (50 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by normal phase silica gel chromatography (0–100% EtOAc:hexanes) gave 5-bromo-2-(1-methanesulfonylcyclopropyl)pyrimidine. ^1H NMR (500 MHz, $CDCl_3$): δ 8.74 (s, 2H), 3.36 (s, 3H), 2.03–1.98 (m, 2H), 1.79–1.75 (m, 2H). MS = 277.0 / 279.0 $[M+H]^+$.

Step 4: 2-(1-Methanesulfonylcyclopropyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine



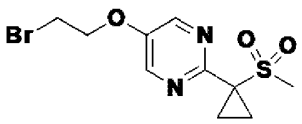
[0799] To a vial equipped with a stir bar were added 5-bromo-2-(1-methanesulfonylcyclopropyl)pyrimidine (500 mg, 1.80 mmol), bis(pinacolato)diboron (687 mg, 2.71 mmol), potassium acetate (619 mg, 6.31 mmol), 1,1'-bis(diphenylphosphino)ferrocene palladium dichloride (66 mg, 0.09 mmol), and dry 1,4-dioxane (9.0 mL). The vial was sealed and evacuated until gas evolution from the solution was observed. The vial was then filled with N_2 and evacuated. This process was repeated three times, and the sealed vial was then heated at 100 °C for 16 h. The reaction mixture was allowed to cool to room temperature and was then diluted with EtOAc (20 mL). The mixture was filtered through Celite, and the filtrate was concentrated in vacuo to provide 2-(1-methanesulfonylcyclopropyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine, which was used in the subsequent step without further purification.

Step 5: 2-(1-Methanesulfonylcyclopropyl)pyrimidin-5-ol



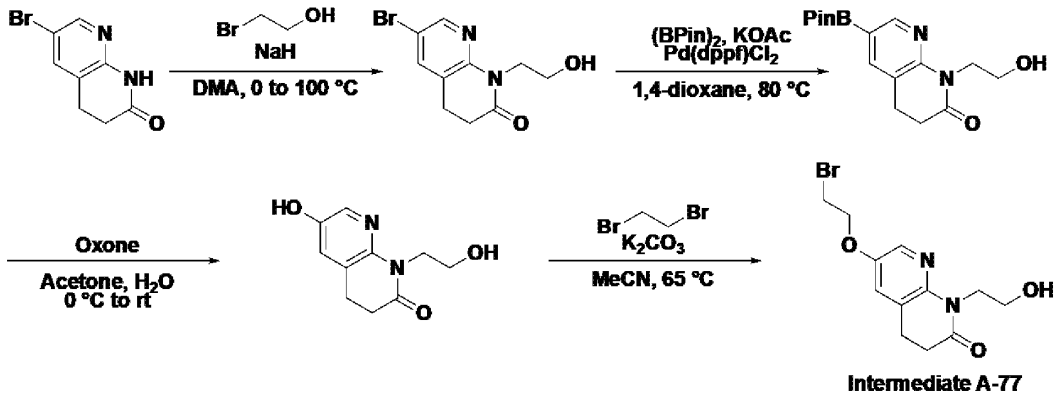
[0800] To a vial containing a solution of 2-(1-methanesulfonylcyclopropyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (300 mg, 0.93 mmol) in MeOH (3.1 mL) was added 30% hydrogen peroxide in H_2O (0.284 mL, 2.78 mmol) dropwise. The mixture was allowed to stir for 2 h. The reaction mixture was concentrated in vacuo, diluted with MeOH, and concentrated in vacuo. The resulting mixture was diluted with MeOH and concentrated to give 2-(1-methanesulfonylcyclopropyl)pyrimidin-5-ol, which was used in the subsequent step without further purification. MS = 215.04 $[M+H]^+$.

Step 6: 5-(2-Bromoethoxy)-2-(1-methanesulfonylcyclopropyl)pyrimidine



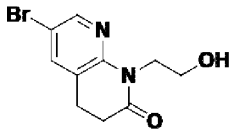
[0801] A vial was charged with 2-(1-methanesulfonylcyclopropyl)pyrimidin-5-ol (200 mg, 0.934 mmol) and dissolved in 1,2-dibromoethane (3.1 mL, 41 mmol) and DMF (0.5 mL). Cs_2CO_3 (0.912 g, 2.801 mmol) was added, and the reaction mixture was heated at 100 °C for 6 h. After cooling to room temperature, the reaction mixture was then filtered over Celite and concentrated in vacuo to afford 5-(2-bromoethoxy)-2-(1-methanesulfonylcyclopropyl)pyrimidine (**Intermediate A-76**), which was carried onto the next step without further purification. MS = 321.1 / 323.1 $[M+H]^+$.

General Procedure for Intermediate A-77



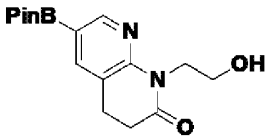
Intermediate A-77

Step 1: 6-bromo-1-(2-hydroxyethyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



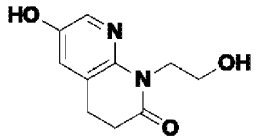
[0802] To a 0 °C solution of 6-bromo-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (4.00 g, 17.6 mmol) in DMA (80 mL) under N_2 atmosphere was added NaH (3.52 g, 60 wt% in mineral oil, 88.1 mmol). After stirring for 15 min, 2-bromoethanol (22.0 g, 176 mmol) was added dropwise. The reaction mixture was heated to 100 °C and stirred for 16 h. The reaction mixture was cooled to 0 °C, quenched with H_2O (40 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 40 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 40 g cartridge, 0–45% EtOAc:petroleum ether) to give 6-bromo-1-(2-hydroxyethyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one. MS = 271.0 / 273.0 $[M+H]^+$.

Step 2: 1-(2-hydroxyethyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



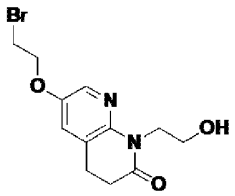
[0803] To a mixture of 6-bromo-1-(2-hydroxyethyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (2.00 g, 7.38 mmol) and bis(pinacolato)diboron (2.25 g, 8.85 mmol) in 1,4-dioxane (30 mL) was added KOAc (1.45 g, 14.8 mmol). The mixture was degassed and purged with N_2 (3x). $Pd(dppf)Cl_2$ (540 mg, 0.738 mmol) was added, then the mixture was heated to 80 °C and stirred for 16 h under N_2 atmosphere. After cooling to room temperature, the reaction mixture was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 0–30% EtOAc:petroleum ether) to give 1-(2-hydroxyethyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one. MS = 319.2.0 $[M+H]^+$.

Step 3: 6-hydroxy-1-(2-hydroxyethyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



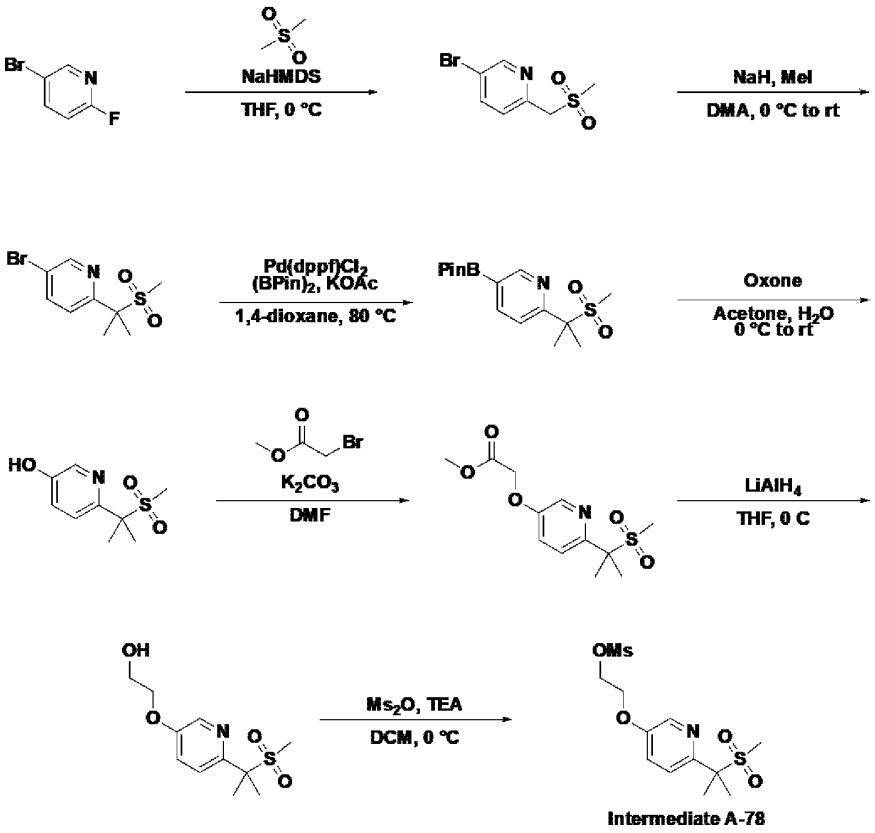
[0804] To a 0 °C solution of 1-(2-hydroxyethyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (1.60 g, 5.03 mmol) in acetone (10 mL) and H_2O (10 mL) was added Oxone (3.71 g, 6.03 mmol). The mixture was stirred at room temperature for 2 h. The reaction mixture was cooled to 0 °C, quenched with saturated aqueous Na_2SO_3 (40 mL), and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with saturated aqueous Na_2SO_3 (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give 6-hydroxy-1-(2-hydroxyethyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one, which was used in the subsequent step without further purification. MS = 209.1 $[M+H]^+$.

Step 4: 6-(2-bromoethoxy)-1-(2-hydroxyethyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one

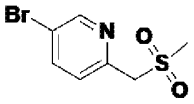


[0805] A mixture of 6-hydroxy-1-(2-hydroxyethyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (200 mg, 0.961 mmol), 1,2-dibromoethane (1.45 mL, 19.2 mmol) and K_2CO_3 (664 mg, 4.80 mmol) in MeCN (3 mL) was stirred at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 0–30% EtOAc:petroleum ether) to give 6-(2-bromoethoxy)-1-(2-hydroxyethyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (**Intermediate A-77**). MS = 315.1 / 317.1 $[M+H]^+$.

General Procedure for Intermediate A-78

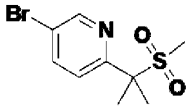


Step 1: 5-bromo-2-(methanesulfonylmethyl)pyridine



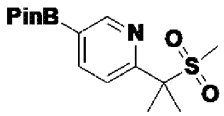
[0806] To a 0 °C solution of DMSO (11.5 mL, 142 mmol) in THF (100 mL) under N_2 atmosphere was added 1.0 M NaHMDS in THF (142 mL, 142 mmol) dropwise. The mixture was stirred at 0 °C for 1 h, then a solution of 5-bromo-2-fluoropyridine (2.92 mL, 28.4 mmol) in THF (50 mL) was added dropwise, and the mixture was stirred for another 1 h. The reaction mixture was quenched with H_2O (40 mL) and then extracted with EtOAc (3 x 50 mL. The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by reverse phase preparative HPLC (Agela C_{18} column, 20–50% MeCN in water with 0.1% NH_4OH modifier) afforded 5-bromo-2-(methanesulfonylmethyl)pyridine. MS = 250.0 / 252.0 $[M+H]^+$.

Step 2: 5-bromo-2-(2-methanesulfonylpropan-2-yl)pyridine



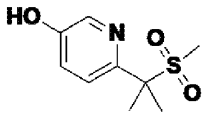
[0807] To a 0 °C solution of 5-bromo-2-(methanesulfonylmethyl)pyridine (3.00 g, 12.0 mmol) in DMA (30 mL) under N_2 atmosphere was added NaH (1.06 g, 60 wt% in mineral oil, 26.4 mmol) portionwise. After stirring at 0° C for 1 h, a solution of MeI (2.24 mL, 36.0 mmol, 2.24 mL) in DMA (30 mL) was added dropwise. The mixture was allowed to warm to room temperature and stirred for another 12 h. The mixture was cooled to 0 °C, quenched with H_2O (40 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 40 g cartridge, 0–40% EtOAc:petroleum ether) to give 5-bromo-2-(2-methanesulfonylpropan-2-yl)pyridine. MS = 278.1 / 280.1 $[M+H]^+$.

Step 3: 2-(2-methanesulfonylpropan-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine



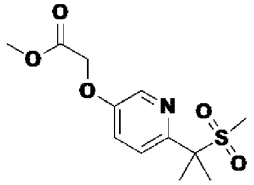
[0808] To a mixture of 5-bromo-2-(2-methanesulfonylpropan-2-yl)pyridine (2.40 g, 8.63 mmol), bis(pinacolato)diboron (3.29 g, 12.9 mmol) in 1,4-dioxane (10 mL) was added KOAc (1.69 g, 17.3 mmol). The mixture was degassed and purged with N_2 (3x), and then the $Pd(dppf)Cl_2$ (316 mg, 0.431 mmol) was added. The mixture was heated to 80 °C and stirred for 12 h under N_2 atmosphere. The reactions mixture was cooled to room temperature, was diluted with H_2O (40 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layers washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 40 g cartridge, 0–40% EtOAc:petroleum ether) to give 2-(2-methanesulfonylpropan-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine. MS = 326.2 $[M+H]^+$.

Step 4: 6-(2-methanesulfonylpropan-2-yl)pyridin-3-ol



[0809] To a 0 °C solution of 2-(2-methanesulfonylpropan-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (900 mg, 2.77 mmol) in acetone (10 mL) and H_2O (10 mL) was added Oxone (3.40 g, 5.53 mmol). The mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was cooled to 0 °C and quenched with saturated aqueous Na_2SO_3 (50 mL), then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 40 g cartridge, 0–40% EtOAc:petroleum ether) to give 6-(2-methanesulfonylpropan-2-yl)pyridin-3-ol. MS = 216.1 $[M+H]^+$.

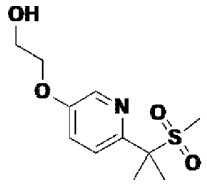
Step 5: methyl 2-{[6-(2-methanesulfonylpropan-2-yl)pyridin-3-yl]oxy}acetate



[0810] To a solution of 6-(2-methanesulfonylpropan-2-yl)pyridin-3-ol (300 mg, 1.39 mmol) in DMF (6 mL) were added K_2CO_3 (385 mg, 2.79 mmol) and methyl 2-bromoacetate (255 mg, 1.67 mmol). The mixture was stirred at room temperature. The mixture was quenched with H_2O (20 mL)

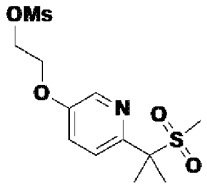
and then extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 40 g cartridge, 0–40% EtOAc:petroleum ether) to give methyl 2-{[6-(2-methanesulfonylpropan-2-yl)pyridin-3-yl]oxy}acetate. MS = 288.1 $[M+H]^+$.

Step 6: 2-{[6-(2-methanesulfonylpropan-2-yl)pyridin-3-yl]oxy}ethan-1-ol



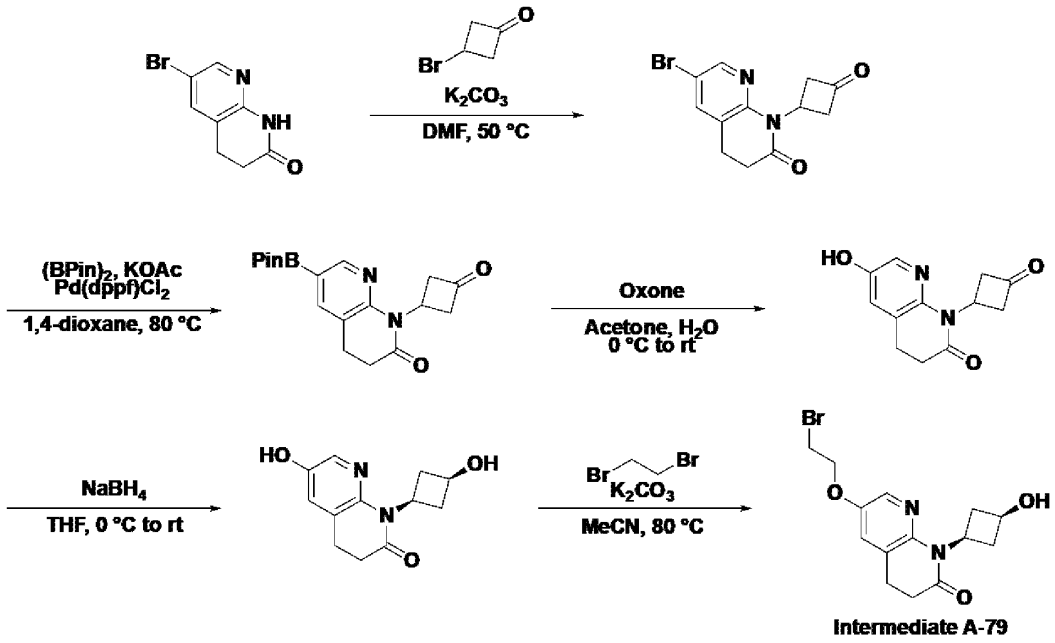
[0811] To a 0 °C solution of methyl 2-{[6-(2-methanesulfonylpropan-2-yl)pyridin-3-yl]oxy}acetate (400 mg, 1.39 mmol) in THF (8 mL) under N_2 atmosphere was added $LiAlH_4$ (79.3 mg, 2.09 mmol). The mixture was stirred at 0 °C for 2 h. The mixture was quenched with H_2O (20 mL) and then extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (2 x 20 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo to give methyl 2-{[6-(2-methanesulfonylpropan-2-yl)pyridin-3-yl]oxy}acetate, which was used in the subsequent step without further purification. MS = 260.1 $[M+H]^+$.

Step 7: 2-{[6-(2-methanesulfonylpropan-2-yl)pyridin-3-yl]oxy}ethyl methanesulfonate

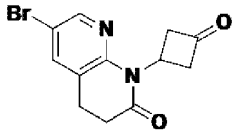


[0812] To a 0 °C solution of methyl 2-{[6-(2-methanesulfonylpropan-2-yl)pyridin-3-yl]oxy}acetate (361 mg, 1.39 mmol) in DCM (5 mL) was added methanesulfonic anhydride (364 mg, 2.09 mmol) and TEA (388 µL, 2.78 mmol). The mixture was warmed to room temperature and stirred for 2 h. The mixture was quenched with H_2O (10 mL) and then extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 10 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo to give 2-{[6-(2-methanesulfonylpropan-2-yl)pyridin-3-yl]oxy}ethyl methanesulfonate (**Intermediate A-78**). MS = 338.1 $[M+H]^+$

General Procedure for Intermediate A-79

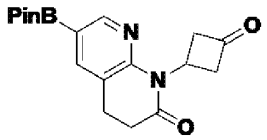


Step 1: 6-bromo-1-(3-oxocyclobutyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



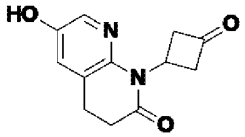
[0813] To a solution of 6-bromo-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (250 mg, 1.10 mmol) in DMF (5 mL) under N_2 atmosphere was added K_2CO_3 (380 mg, 2.75 mmol). The mixture was stirred at 50 °C for 4 h, and then a solution of 3-bromocyclobutanone (197 mg, 1.32 mmol) in DMF (5 mL) was added to the reaction mixture. The mixture was stirred at 50 °C for an additional 1 h. After cooling to room temperature, the mixture was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–50% EtOAc:petroleum ether) to give 6-bromo-1-(3-oxocyclobutyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one. MS = 295.1 / 297.1 $[M+H]^+$.

Step 2: 1-(3-oxocyclobutyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



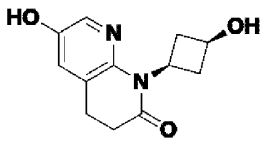
[0814] A mixture of 6-bromo-1-(3-oxocyclobutyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (1.20 g, 4.07 mmol), bis(pinacolato)diboron (1.24 g, 4.88 mmol), KOAc (798 mg, 8.13 mmol) and Pd(dppf)Cl_2 (149 mg, 0.203 mmol) in 1,4-dioxane (60 mL) was degassed and purged with N_2 (3x). The mixture was stirred at 80 °C for 12 h under N_2 atmosphere. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo to provide 1-(3-oxocyclobutyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one, which was used into the next step without further purification. MS = 343.2 $[M+H]^+$.

Step 3: 6-hydroxy-1-(3-oxocyclobutyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



[0815] To a 0 °C solution of 1-(3-oxocyclobutyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (1.00 g, 2.92 mmol) in acetone (30 mL) and H_2O (30 mL) was added Oxone (3.59 g, 5.84 mmol). The mixture was stirred at room temperature for 2 h. The mixture was quenched with H_2O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–100% EtOAc:petroleum ether) to give 6-hydroxy-1-(3-oxocyclobutyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one. MS = 233.2 $[M+H]^+$.

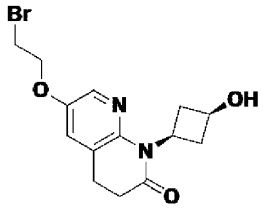
Step 4: 6-hydroxy-1-[(*cis*)-3-hydroxycyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



[0816] To a 0 °C solution of 6-hydroxy-1-(3-oxocyclobutyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (500 mg, 2.15 mmol) in THF (15 mL) under N_2 atmosphere was added NaBH4 (163 mg, 4.31 mmol). The mixture was stirred at room temperature for 2 h, and then was quenched

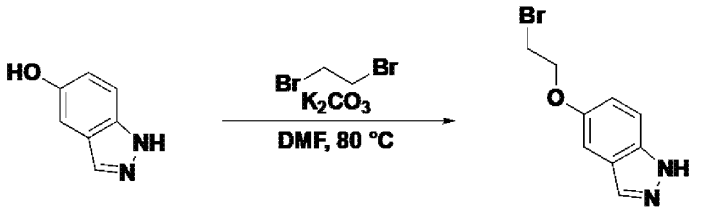
with saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 30 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–50% EtOAc:petroleum ether) to give 6-hydroxy-1-[(*cis*)-3-hydroxycyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one. MS = 235.2 $[M+H]^+$.

Step 5: 6-(2-bromoethoxy)-1-[(*cis*)-3-hydroxycyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



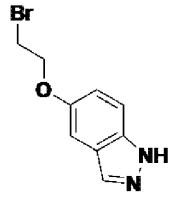
[0817] To a solution of 6-hydroxy-1-[(*cis*)-3-hydroxycyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (300 mg, 1.28 mmol) in MeCN (4 mL) was added K_2CO_3 (531 mg, 3.84 mmol) and 1,2-dibromoethane (3.86 mL, 51.23 mmol). The mixture was stirred at 80 °C for 12 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–50% EtOAc:petroleum ether) to give 6-(2-bromoethoxy)-1-[(*cis*)-3-hydroxycyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (**Intermediate A-79**). MS = 341.1 / 343.1 $[M+H]^+$.

General Procedure for Intermediate A-80



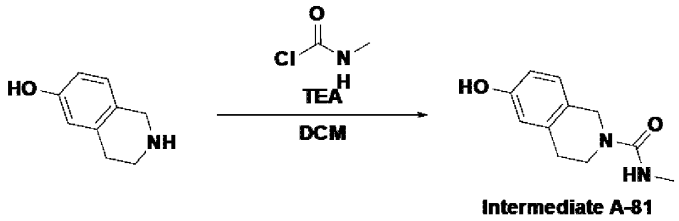
Intermediate A-80

Step 1: 5-(2-bromoethoxy)-1H-indazole



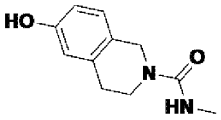
[0818] A solution of 1H-indazol-5-ol (1.00 g, 7.46 mmo), 1,2-dibromoethane (11.3 mL, 149 mmol), and K_2CO_3 (1.24 g, 8.95 mmol) in DMF (10 mL) was stirred at 80 °C for 16 h. After cooling to room temperature, the mixture was diluted with H_2O (10 mL), then extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 10 g cartridge, 0–100% EtOAc:petroleum ether) to give 5-(2-bromoethoxy)-1H-indazole (**Intermediate A-80**). MS = 241.1 / 243.1 $[M+H]^+$.

General Procedure for Intermediate A-81



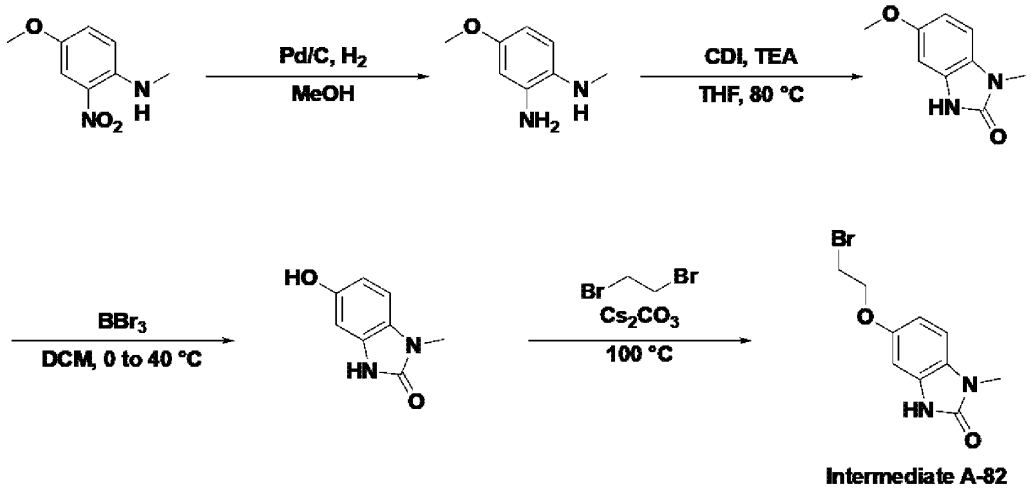
Intermediate A-81

Step 1: 6-hydroxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline-2-carboxamide

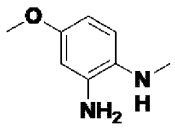


[0819] To a solution of 1,2,3,4-tetrahydroisoquinolin-6-ol (500 mg, 3.35 mmol) in DCM (7 mL) was added TEA (847 mg, 8.38 mmol) followed by the dropwise addition of *N*-methylcarbamoyl chloride (783 mg, 8.38 mmol). The mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 4 g cartridge, 0–100% EtOAc:petroleum ether) to give 6-hydroxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline-2-carboxamide (**Intermediate A-81**). MS = 207.2 $[M+H]^+$.

General Procedure for Intermediate A-82

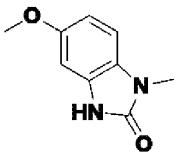


Step 1: 4-methoxy-*N*1-methylbenzene-1,2-diamine



[0820] To a solution of 4-methoxy-*N*-methyl-2-nitroaniline (500 mg, 2.74 mmol) in MeOH (10 mL) under N_2 atmosphere was added Pd/C (150 mg, 10 wt%, 0.141 mmol). The suspension was degassed under vacuum and purged with H_2 (3x). After stirring under an atmosphere of H_2 (15 psi) at room temperature for 12 h, solids were removed by filtration through Celite and the filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 0–50% EtOAc:petroleum ether) to give 4-methoxy-*N*1-methylbenzene-1,2-diamine. MS = 153.2 $[M+H]^+$.

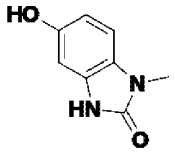
Step 2: 5-methoxy-1-methyl-2,3-dihydro-1H-1,3-benzodiazol-2-one



[0821] To a solution of 4-methoxy-*N*1-methylbenzene-1,2-diamine (150 mg, 0.986 mmol) in THF (20 mL) were added TEA (99.0 mg, 0.986 mmol) and CDI (799 mg, 4.93 mmol). The mixture was stirred at 80 °C for 12 h under N_2 atmosphere. After cooling to room temperature, solids were

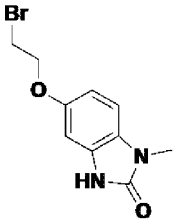
removed by filtration and the filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–100% EtOAc:petroleum ether) to give 5-methoxy-1-methyl-2,3-dihydro-1H-1,3-benzodiazol-2-one. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.72 (s, 1H), 6.96 (d, J = 8.4 Hz, 1H), 6.61–6.56 (m, 2H), 3.71 (s, 3H), 3.23 (s, 3H).

Step 3: 5-hydroxy-1-methyl-2,3-dihydro-1H-1,3-benzodiazol-2-one



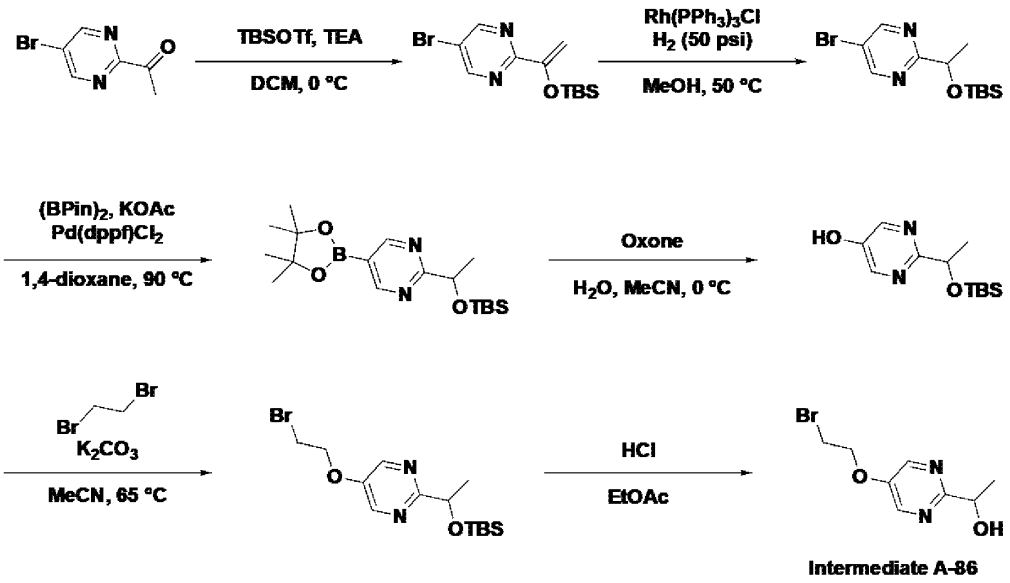
[0822] To a 0 °C solution of 5-methoxy-1-methyl-2,3-dihydro-1H-1,3-benzodiazol-2-one (216 mg, 1.21 mmol) in DCM (5 mL) was added BBr_3 (1.52 g, 6.06 mmol) dropwise. The mixture was stirred at 40 °C for 4 h. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 4 g cartridge, 0–100% EtOAc:petroleum ether) to give 5-methoxy-1-methyl-2,3-dihydro-1H-1,3-benzodiazol-2-one.

Step 4: 5-(2-bromoethoxy)-1-methyl-2,3-dihydro-1H-1,3-benzodiazol-2-one

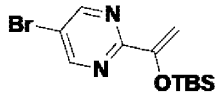


[0823] A mixture of 5-methoxy-1-methyl-2,3-dihydro-1H-1,3-benzodiazol-2-one (100 mg, 0.609 mmol) and Cs_2CO_3 (595 mg, 1.83 mmol) in 1,2-dibromoethane (5 mL, 66 mmol) under N_2 atmosphere was stirred at 80 °C for 12 h. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 4 g cartridge, 0–100% EtOAc:petroleum ether) to give 5-(2-bromoethoxy)-1-methyl-2,3-dihydro-1H-1,3-benzodiazol-2-one (**Intermediate A-82**). MS = 271.0 / 273.0 $[M+H]^+$.

General Procedure for Intermediate A-86

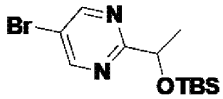


Step 1: 5-bromo-2-{1-[(*tert*-butyldimethylsilyl)oxy]ethenyl}pyrimidine



[0824] To a solution of 1-(5-bromopyrimidin-2-yl)ethan-1-one (500 mg, 2.49 mmol) in DCM (10 mL) were added TEA (378 mg, 3.73 mmol) and TBSOTf (988 mg, 3.73 mmol). The mixture was stirred at 0 °C for 0.5 h. The reaction mixture was quenched with H_2O (10 mL) and then extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–20% EtOAc:Petroleum ether) to give 5-bromo-2-{1-[(*tert*-butyldimethylsilyl)oxy]ethenyl}pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.99 (s, 2H), 5.80 (s, 1H), 4.89 (s, 1H), 0.96 (s, 9H), 0.16 (s, 6H).

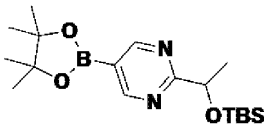
Step 2: 5-bromo-2-{1-[(*tert*-butyldimethylsilyl)oxy]ethyl}pyrimidine



[0825] To a solution of 5-bromo-2-{1-[(*tert*-butyldimethylsilyl)oxy]ethenyl}pyrimidine (300 mg, 0.952 mmol) in MeOH (30 mL) under N_2 atmosphere was added $Rh(PPh_3)_3Cl$ (178 mg, 0.190 mmol). The suspension was degassed under vacuum and purged with H_2 several times. The mixture

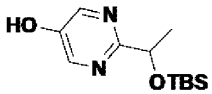
was stirred under H_2 (50 psi) at 50 °C for 4 h. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–10% EtOAc:Petroleum ether) to give 5-bromo-2-{1-[(*tert*-butyldimethylsilyl)oxy]ethyl}pyrimidine. MS = 317.1 / 319.1 $[M+H]^+$.

Step 3: 2-{1-[(*tert*-butyldimethylsilyl)oxy]ethyl}-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine



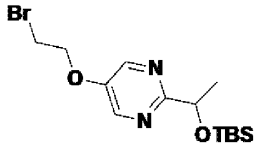
[0826] A mixture of 5-bromo-2-{1-[(*tert*-butyldimethylsilyl)oxy]ethyl}pyrimidine (0.25 g, 0.788 mmol), bis(pinacolato)diboron (240 mg, 0.945 mmol), KOAc (232 mg, 2.36 mmol), and Pd(dppf)Cl_2 (58 mg, 78.8 µmol) in 1,4-dioxane (15 mL) was degassed and purged with N_2 (3x). The mixture was stirred at 90 °C for 5 h under N_2 atmosphere. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo to give 2-{1-[(*tert*-butyldimethylsilyl)oxy]ethyl}-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine, which was used in the subsequent step without further purification.

Step 4: 2-{1-[(*tert*-butyldimethylsilyl)oxy]ethyl}pyrimidin-5-ol



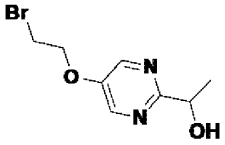
[0827] To a 0 °C solution of 2-{1-[(*tert*-butyldimethylsilyl)oxy]ethyl}-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (300 mg, 0.823 mmol) in MeCN (10 mL) and H_2O (10 mL) was added Oxone (607 mg, 0.988 mmol). The mixture was stirred at 0 °C for 1 h, then was quenched with saturated aqueous Na_2SO_3 (5 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (15 mL), saturated aqueous Na_2SO_3 (15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–100% EtOAc:Petroleum ether) to give 2-{1-[(*tert*-butyldimethylsilyl)oxy]ethyl}pyrimidin-5-ol. MS= 255.2 $[M+H]^+$.

Step 5: 5-(2-bromoethoxy)-2-{1-[(*tert*-butyldimethylsilyl)oxy]ethyl}pyrimidine



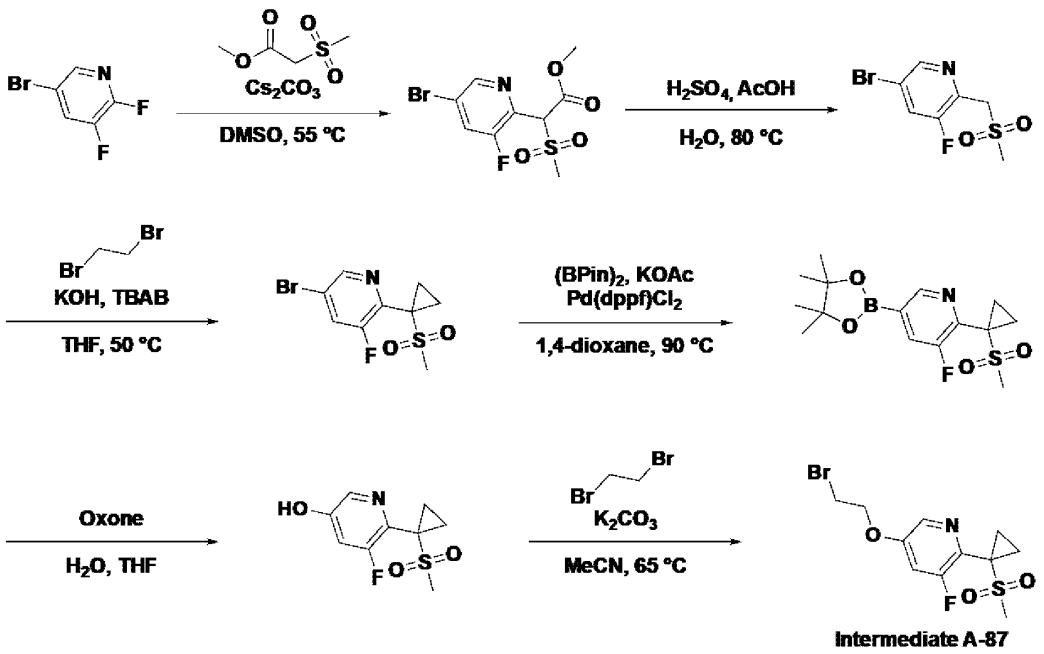
[0828] To a solution of 2-{1-[(*tert*-butyldimethylsilyl)oxy]ethyl}pyrimidin-5-ol (80.0 mg, 0.314 mmol) in MeCN (3 mL) was added K_2CO_3 (218 mg, 1.57 mmol) and 1,2-dibromoethane (2.36 g, 12.6 mmol). The mixture was stirred at 65 °C for 16 h. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 4 g cartridge, 0–30% EtOAc:Petroleum ether) to give 5-(2-bromoethoxy)-2-{1-[(tert-butyldimethylsilyl)oxy]ethyl}pyrimidine. 5-(2-bromoethoxy)-2-(1-((*tert*-butyldimethylsilyl)oxy)ethyl)pyrimidine. MS = 361.1 / 363.1 $[M+H]^+$

Step 6: 1-[5-(2-bromoethoxy)pyrimidin-2-yl]ethan-1-ol

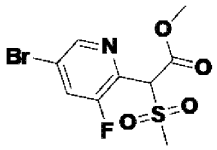


[0829] To a solution of 5-(2-bromoethoxy)-2-(1-((*tert*-butyldimethylsilyl)oxy)ethyl)pyrimidine (130 mg, 0.360 mmol) in EtOAc (3 mL) was added 4.0 M HCl in EtOAc (10 mL, 40.0 mmol). The mixture was stirred at room temperature for 5 h. The mixture was concentrated in vacuo to give 1-[5-(2-bromoethoxy)pyrimidin-2-yl]ethan-1-ol (**Intermediate A-86**), which was used in the subsequent steps without further purification. MS= 247.0 / 249.0 $[M+H]^+$.

General Procedure for Intermediate A-87

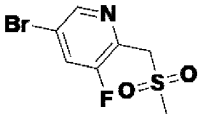


Step 1: methyl 2-(5-bromo-3-fluoropyridin-2-yl)-2-methanesulfonylacetate



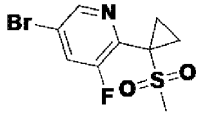
[0830] To a solution of 5-bromo-2,3-difluoropyridine (5.00 g, 25.8 mmol) in DMSO (55 mL) was added Cs_2CO_3 (16.8 g, 51.6 mmol) and methyl 2-methylsulfonylacetate (4.71 g, 30.9 mmol). The mixture was stirred at 55 °C for 30 h. After cooling to room temperature, the reaction mixture was quenched with H_2O (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 40 g cartridge, 0–25% EtOAc:Petroleum ether) to give methyl 2-(5-bromo-3-fluoropyridin-2-yl)-2-methanesulfonylacetate. MS = 325.8 / 327.8 $[M+H]^+$.

Step 2: 5-bromo-3-fluoro-2-(methanesulfonylmethyl)pyridine



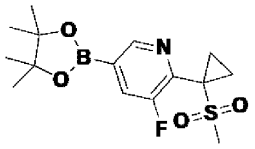
[0831] To a solution of methyl 2-(5-bromo-3-fluoropyridin-2-yl)-2-methanesulfonylacetate (5.30 g, 16.3 mmol) in H_2O (26 mL) and AcOH (26 mL) was added H_2SO_4 (5.10 mL, 95.8 mmol). The mixture was stirred at 80 °C for 15 h. After cooling to room temperature, the reaction mixture was adjusted to pH = 4.0 with saturated aqueous Na_2CO_3. The mixture was extracted with EtOAc (3 x 25 mL), the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give crude 5-bromo-3-fluoro-2-(methanesulfonylmethyl)pyridine, which was used in the subsequent step without further purification. MS = 267.8 / 269.8 $[M+H]^+$.

Step 3: 5-bromo-3-fluoro-2-(1-methanesulfonylcyclopropyl)pyridine



[0832] To a solution of 5-bromo-3-fluoro-2-(methanesulfonylmethyl)pyridine (3.30 g, 12.3 mmol) in THF (35 mL) were added KOH (3.45 g, 61.5 mmol), 1,2-dibromoethane (13.9 g, 73.9 mmol) and TBAB (793 mg, 2.46 mmol). The mixture was stirred at 50 °C for 24 h. After cooling to room temperature, the reaction mixture was quenched with H_2O (30 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 20 g cartridge, 0–30% EtOAc:Petroleum ether) to give 5-bromo-3-fluoro-2-(1-methanesulfonylcyclopropyl)pyridine. MS = 293.9 / 295.9 $[M+H]^+$.

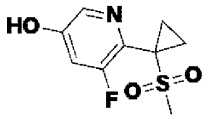
Step 4: 3-fluoro-2-(1-methanesulfonylcyclopropyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine



[0833] To a solution of 5-bromo-3-fluoro-2-(1-methanesulfonylcyclopropyl)pyridine (500 mg, 1.70 mmol) in 1,4-dioxane (6 mL) under N_2 atmosphere was added bis(pinacolato)diboron (648 mg, 2.55 mmol), KOAc (334 mg, 3.40 mmol) and $Pd(dppf)Cl_2$ (125 mg, 0.170 mmol). The mixture was stirred at 90 °C for 15 h under N_2 atmosphere. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo. The crude residue was purified by

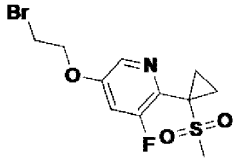
flash silica gel chromatography (Biotage 20 g cartridge, 0–55% EtOAc:Petroleum ether) to give 3-fluoro-2-(1-methanesulfonylcyclopropyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine.

Step 5: 5-fluoro-6-(1-methanesulfonylcyclopropyl)pyridin-3-ol



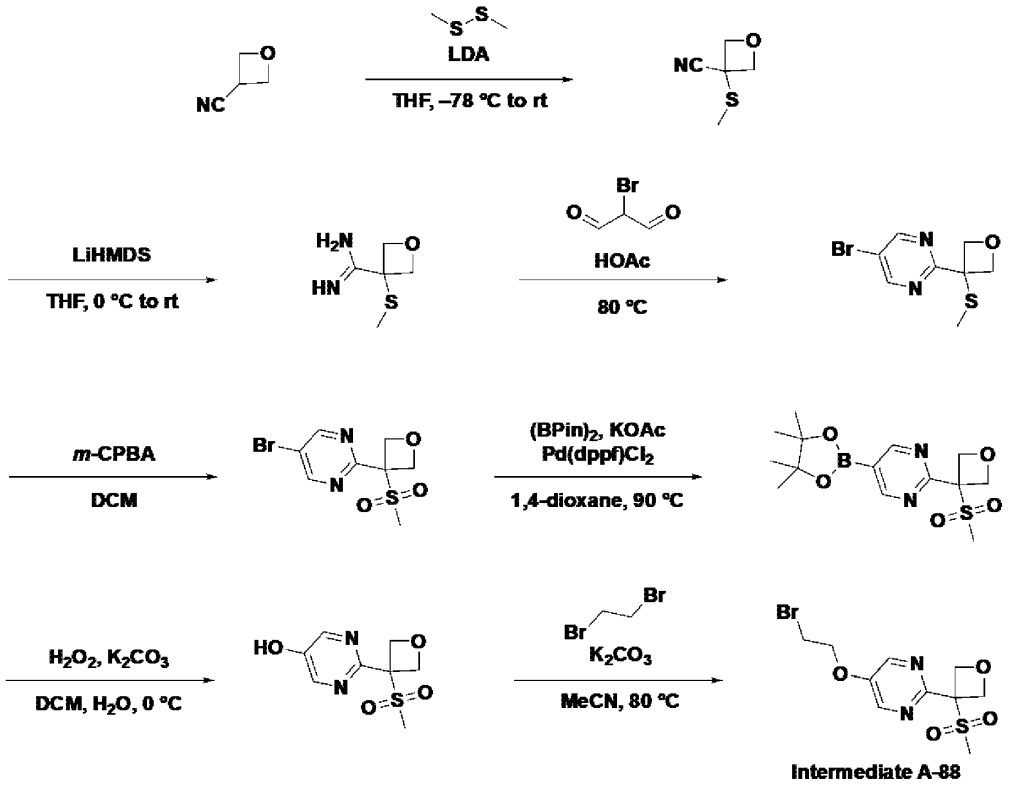
[0834] To a solution of 3-fluoro-2-(1-methanesulfonylcyclopropyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (400 mg, 1.17 mmol) in H_2O (3 mL) and THF (3 mL) was added Oxone (721 mg, 1.17 mmol). The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with H_2O (15 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–70% EtOAc:Petroleum ether) to give 5-fluoro-6-(1-methanesulfonylcyclopropyl)pyridin-3-ol. MS = 232.0 $[M+H]^+$.

Step 6: 5-(2-bromoethoxy)-3-fluoro-2-(1-methanesulfonylcyclopropyl)pyridine

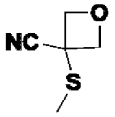


[0835] To a solution of 5-fluoro-6-(1-methanesulfonylcyclopropyl)pyridin-3-ol (140 mg, 0.605 mmol) in MeCN (2 mL) were added 1,2-dibromoethane (4.55 g, 24.2 mmol) and K_2CO_3 (419 mg, 3.03 mmol). The mixture was stirred at 65 °C for 15 h. After cooling to room temperature, the reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 4 g cartridge, 0–40% EtOAc:Petroleum ether) to give 5-(2-bromoethoxy)-3-fluoro-2-(1-methanesulfonylcyclopropyl)pyridine (**Intermediate A-87**). MS=337.9 / 339.9 $[M+H]^+$.

General Procedure for Intermediate A-88

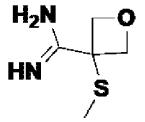


Step 1: 3-(methylsulfanyl)oxetane-3-carbonitrile



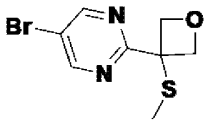
[0836] To a –78 °C solution of oxetane-3-carbonitrile (10.0 g, 12.4 mmol) and (methyldisulfanyl)methane (21.6 mL, 241 mmol) in THF (100 mL) under N_2 atmosphere was added 2.0 M LDA in THF (151 mL, 302 mmol) dropwise. The mixture was warmed to room temperature and stirred for 3 h. The reaction mixture was cooled to 0 °C and then quenched with H_2O (200 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 120 g cartridge, 0–25% EtOAc:Petroleum ether) to give 3-(methylsulfanyl)oxetane-3-carbonitrile. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.13 (d, J = 6.8 Hz, 2H), 4.64 (d, J = 6.8 Hz, 2H), 2.31 (s, 3H).

Step 2: 3-(methylsulfanyl)oxetane-3-carboximidamide



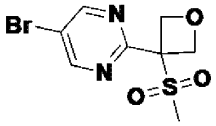
[0837] To a 0 °C solution of 3-(methylsulfanyl)oxetane-3-carbonitrile (2.50 g, 19.4 mmol) in THF (30 mL) under N_2 atmosphere was added 1.0 M LiHMDS in THF (96.8 mL, 96.8 mmol). The mixture was allowed to warm to room temperature and stirred for 15 h, then was quenched with AcOH (40 mL). The resulting solids were isolated by filtration and dried in vacuo to give 3-(methylsulfanyl)oxetane-3-carboximidamide, which was used in the subsequent step without further purification. MS = 147.2 $[M+H]^+$.

Step 3: 5-bromo-2-[3-(methylsulfanyl)oxetan-3-yl]pyrimidine



[0838] A mixture of 3-(methylsulfanyl)oxetane-3-carboximidamide (2.50 g, 17.1 mmol) and 2-bromopropanedial (5.16 g, 34.2 mmol) in AcOH (50 mL) was stirred at 80 °C for 8 h. After cooling to room temperature, the reaction mixture was quenched with H_2O (50 mL), and then extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with saturated aqueous Na_2CO_3 (2 x 50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 20 g cartridge, 0–20% EtOAc:Petroleum ether) to give 5-bromo-2-[3-(methylsulfanyl)oxetan-3-yl]pyrimidine. MS = 261.1 / 263.1 $[M+H]^+$

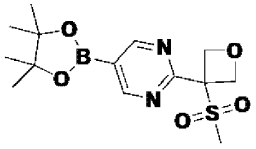
Step 4: 5-bromo-2-(3-methanesulfonyloxetan-3-yl)pyrimidine



[0839] To a solution of 5-bromo-2-[3-(methylsulfanyl)oxetan-3-yl]pyrimidine (150 mg, 0.573 mmol) in DCM (15 mL) was added *m*-CPBA (350 mg, 1.72 mmol, 85% purity). The mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated aqueous Na_2SO_3 (20 mL), diluted with H_2O (10 mL), and extracted with DCM (3 x 15 mL). The combined

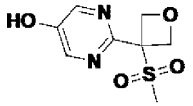
organic layers were washed with saturated aqueous $NaHCO_3$ (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–50% EtOAc:Petroleum ether) to give 5-bromo-2-(3-methanesulfonyloxetan-3-yl)pyrimidine. MS = 293.0 / 295.0 $[M+H]^+$.

Step 5: 2-(3-methanesulfonyloxetan-3-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine



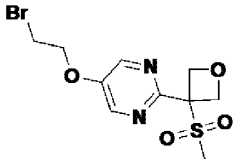
[0840] A mixture of 5-bromo-2-(3-methanesulfonyloxetan-3-yl)pyrimidine (140 mg, 0.476 mmol), bis(pinacolato)diboron (182 mg, 0.718 mmol), KOAc (141 mg, 1.43 mmol), and $Pd(dppf)Cl_2$ (35 mg, 47.8 μmol) in 1,4-dioxane (15 mL) was degassed and purged with N_2 (3x). The mixture was stirred at 90 °C for 15 h under N_2 atmosphere. After cooling to room temperature, solids were removed by filtration, and the filtrate was concentrated in vacuo to give 2-(3-methanesulfonyloxetan-3-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine, which was used in the subsequent step without further purification. MS = 341.2 $[M+H]^+$

Step 6: 2-(3-methanesulfonyloxetan-3-yl)pyrimidin-5-ol



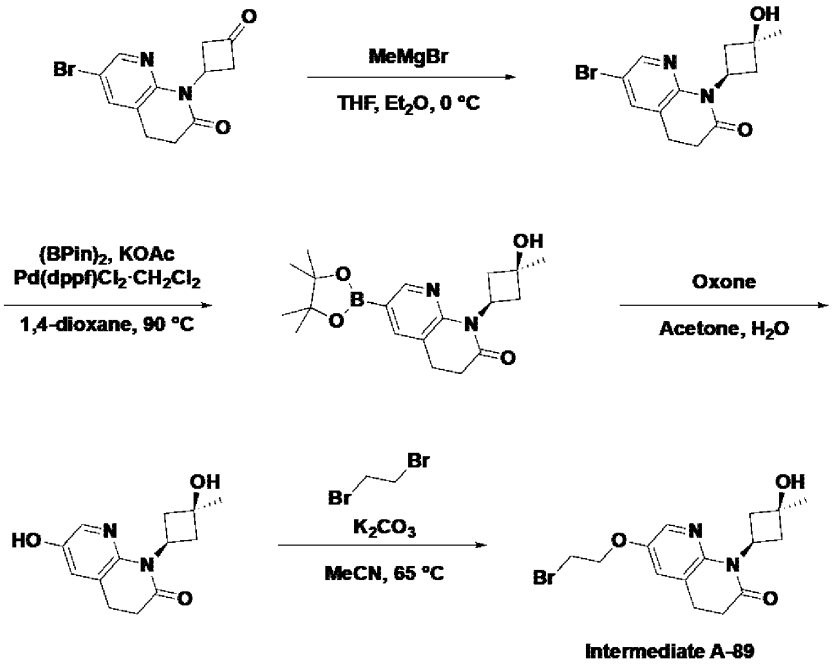
[0841] To a 0 °C solution of 2-(3-methanesulfonyloxetan-3-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (220 mg, 0.646 mmol) in DCM (20 mL) were added K_2CO_3 (179 mg, 0.118 mmol) and 30% H_2O_2 in H_2O (0.25 mL, 2.59 mmol). The mixture was stirred at room temperature for 2 h, then was quenched with saturated aqueous $Na_2S_2O_3$ (5 mL). The mixture was extracted with DCM (2 x 20 mL), the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo give 2-(3-methanesulfonyloxetan-3-yl)pyrimidin-5-ol, which was used in the subsequent step without further purification. MS = 229.0 $[M–H]^+$.

Step 7: 5-(2-bromoethoxy)-2-(3-methanesulfonyloxetan-3-yl)pyrimidine

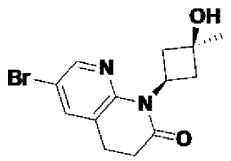


[0842] To a solution of 2-(3-methanesulfonyloxetan-3-yl)pyrimidin-5-ol (220 mg, 0.957 mmol) in MeCN (10 mL) was added K_2CO_3 (660 mg, 4.78 mmol) and 1,2-dibromoethane (7.18 g, 37.5 mmol). The mixture was stirred at 80 °C for 2 h. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–60% EtOAc:Petroleum ether) to give 5-(2-bromoethoxy)-2-(3-methanesulfonyloxetan-3-yl)pyrimidine (**Intermediate A-88**). MS = 336.9 / 338.9 $[M+H]^+$

General Procedure for Intermediate A-89

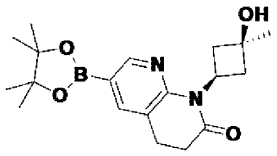


Step 1: 6-bromo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



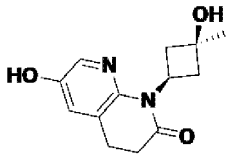
[0843] To a 0 °C solution of 6-bromo-1-(3-oxocyclobutyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (Procedure for Intermediate A-79, Step 1, 1.00 g, 3.39 mmol) in THF (20 mL) was added 3.0 M MeMgBr in Et_2O (1.24 mL, 3.72 mmol). The mixture was stirred at 0 °C for 2 h, and then was quenched with saturated aqueous NH_4Cl solution (100 mL). The biphasic mixture was extracted with EtOAc (3 x 50 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–48% EtOAc:Petroleum ether) to give 6-bromo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (d, J = 2.4 Hz, 1H), 7.90 (d, J = 2.4 Hz, 1H), 4.83 (s, 1H), 4.20 – 4.15 (m, 1H), 2.82 (t, J = 7.2 Hz, 2H), 2.58 – 2.52 (m, 2H), 2.49 – 2.42 (m, 2H), 2.33 – 2.25 (m, 2H), 1.25 (s, 3H). MS = 311.0 / 313.0 $[M+H]^+$.

Step 2: 1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-6-(4,4,5,5-tetramethyl-1,3,2 dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



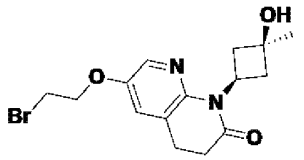
[0844] To a solution of 6-bromo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (1.00 g, 3.21 mmol) in 1,4-dioxane (20 mL) were added bis(pinacolato)diboron (1.06 g, 4.18 mmol), $Pd(dppf)Cl_2$•CH_2Cl_2 (210 mg, 257 μmol) and KOAc (788 mg, 8.03 mmol). The mixture was stirred at 90 °C for 12 h under N_2 atmosphere, and then cooled to room temperature. The mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–58% EtOAc:Petroleum ether) to give 1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one. MS = 359.1 $[M+H]^+$.

Step 3: 6-hydroxy-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



[0845] To a solution of 1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (610 mg, 1.70 mmol) in acetone (10 mL) and H_2O (5 mL) was added Oxone (1.57 g, 2.55 mmol). The mixture was stirred for 2 h, and then was diluted with H_2O (10 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–85% EtOAc:Petroleum ether) to give 6-hydroxy-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one. MS = 249.0 $[M+H]^+$.

Step 4: 6-(2-bromoethoxy)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



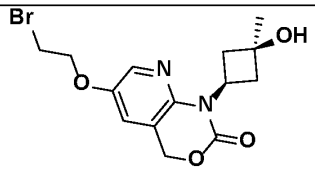
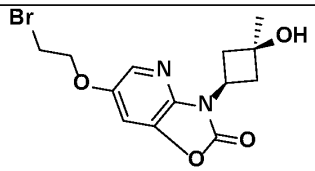
[0846] To a solution of 6-hydroxy-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (400 mg, 1.61 mmol) and 1,2-dibromoethane (1.82 mL, 24.2 mmol) in MeCN (10 mL) was added K_2CO_3 (1.11 g, 8.06 mmol). The mixture was stirred at 65 °C for 12 h. After cooling to room temperature, the mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–70% EtOAc:Petroleum ether) to give 6-(2-bromoethoxy)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (**Intermediate A-89**). ^1H NMR (400 MHz, DMSO-d_6): δ 7.93 (d, J = 2.8 Hz, 1H), 7.39 (d, J = 2.8 Hz, 1H), 4.82 (s, 1H), 4.36 (t, J = 5.6 Hz, 2H), 4.25 – 4.21 (m, 1H), 3.80 (t, J = 5.6 Hz, 2H), 2.79 (t,

J = 6.8 Hz, 2H), 2.51 – 2.49 (m, 2H), 2.47 – 2.41 (m, 2H), 2.34 – 2.33 (m, 2H), 1.25 (s, 3H). MS = 355.0 / 357.0 $[M+H]^+$.

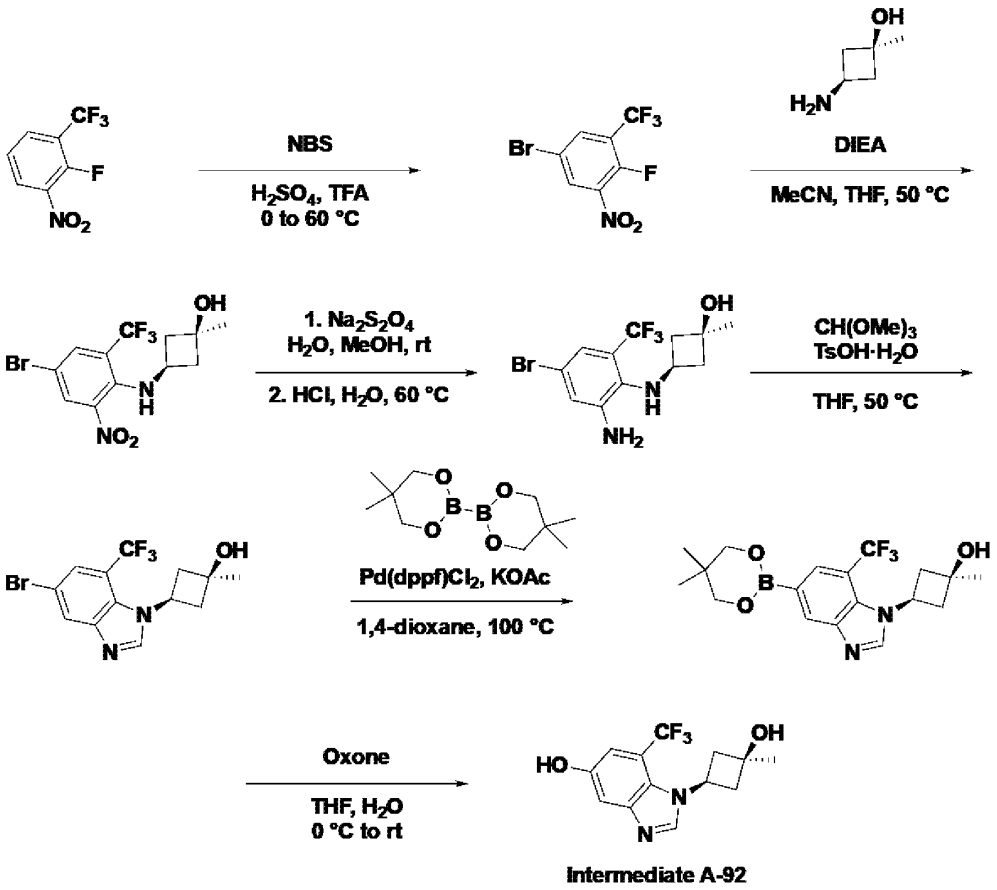
[0847] The following intermediates in Table 11.1 were prepared according to procedures similar those described for **Intermediate A-89** using the appropriate starting materials.

General Procedure for Intermediates A-90 to A-91

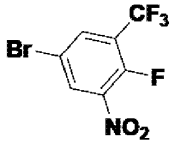
Table 11.1

Intermediate #	Structure	Name	Exact Mass $[M+H]^+$
A-90		6-(2-bromoethoxy)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H,2H,4H-pyrido[2,3-d][1,3]oxazin-2-one	Calc'd 357.0 / 357.0 Found 357.1 / 357.1
A-91		6-(2-bromoethoxy)-3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-2H,3H-[1,3]oxazolo[4,5-b]pyridin-2-one	Calc'd 343.0 / 343.0 Found 343.0 / 343.0

General Procedure for Intermediate A-92



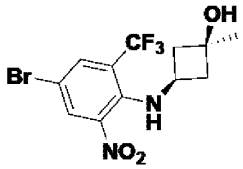
Step 1: 5-bromo-2-fluoro-1-nitro-3-(trifluoromethyl)benzene



[0848] To concentrated H_2SO_4 (15 mL) at 0 °C was added a solution of 2-fluoro-1-nitro-3-(trifluoromethyl)benzene (5.00 g, 23.0 mmol) in TFA (10 mL). NBS (5.11 g, 28.7 mol) was added to the 0 °C mixture in several portions. The mixture was stirred at 60 °C for 16 h. The reaction mixture was cooled to room temperature, and then poured into ice water (200 mL). The mixture was extracted with petroleum ether (2 x 80 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ until pH = 8–9. The organic layer was separated, washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give 5-bromo-2-fluoro-1-nitro-3-

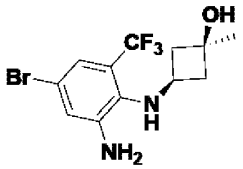
(trifluoromethyl)benzene. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.70 (dd, J = 6.0 Hz, 2.4 Hz, 1H), 8.46 (dd, J = 5.6 Hz, 2.4 Hz, 1H).

Step 2: (*cis*)-3-{[4-bromo-2-nitro-6-(trifluoromethyl)phenyl]amino}-1-methylcyclobutan-1-ol



[0849] A mixture of 5-bromo-2-fluoro-1-nitro-3-(trifluoromethyl)benzene (6.50 g, 22.6 mmol), DIEA (11.2 mL, 67.7 mmol) and (*cis*)-3-amino-1-methylcyclobutan-1-ol (3.42 g, 24.8 mmol, HCl salt) in THF (35 mL) and MeCN (35 mL) was stirred at 50 °C for 2 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was diluted with H_2O (150 mL) and extracted with MTBE (2 x 80 mL). The combined organic layers were washed with brine (80 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give (*cis*)-3-{[4-bromo-2-nitro-6-(trifluoromethyl)phenyl]amino}-1-methylcyclobutan-1-ol, which was used in the subsequent step without further purification. MS = 368.9 / 370.9 $[M+H]^+$.

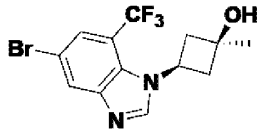
Step 3: (*cis*)-3-{[2-amino-4-bromo-6-(trifluoromethyl)phenyl]amino}-1-methylcyclobutan-1-ol



[0850] To a three-neck round-bottom flask equipped with a magnetic stir bar and a thermometer was added H_2O (170 mL) and sodium dithionite (32.1 g, 184 mmol). To the mixture was added a solution of (*cis*)-3-{[4-bromo-2-nitro-6-(trifluoromethyl)phenyl]amino}-1-methylcyclobutan-1-ol (17.0 g, 46.1 mmol) in MeOH (170 mL) dropwise. The mixture was stirred at room temperature for 1 h, and then 12 M aqueous HCl (35 mL) was added. The mixture was stirred at 60 °C for 1 h. After cooling to room temperature, the mixture was concentrated in vacuo to remove MeOH, and the residue was diluted with H_2O (150 mL). The aqueous layer was adjusted to pH > 7 by addition of solid Na_2CO_3. The mixture was extracted with MTBE (2 x 200 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give

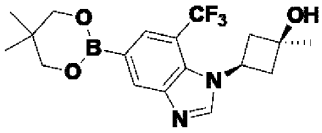
(*cis*)-3-{[2-amino-4-bromo-6-(trifluoromethyl)phenyl]amino}-1-methylcyclobutan-1-ol, which was used in the subsequent step without further purification. MS = 339.0 / 341.0 $[M+H]^+$.

Step 4: (*cis*)-3-[5-bromo-7-(trifluoromethyl)-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol



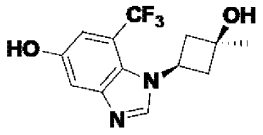
[0851] A mixture of (*cis*)-3-{[2-amino-4-bromo-6-(trifluoromethyl)phenyl]amino}-1-methylcyclobutan-1-ol (13.0 g, 38.3 mmol), trimethoxymethane (6.10 g, 57.5 mmol), and TsOH•H_2O (729 mg, 3.83 mmol) in THF (130 mL) was stirred at 50 °C for 1 h. The mixture was cooled to room temperature and concentrated in vacuo to remove most of the THF. The residual solution was diluted with saturated aqueous $NaHCO_3$ solution (200 mL) and extracted with MTBE (2 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was triturated in MTBE (20 mL) for 30 min. The mixture was filtered to collect the solid to afford (*cis*)-3-[5-bromo-7-(trifluoromethyl)-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol. MS = 349.0 / 350.9 $[M+H]^+$.

Step 5: (*cis*)-3-[5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-7-(trifluoromethyl)-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol



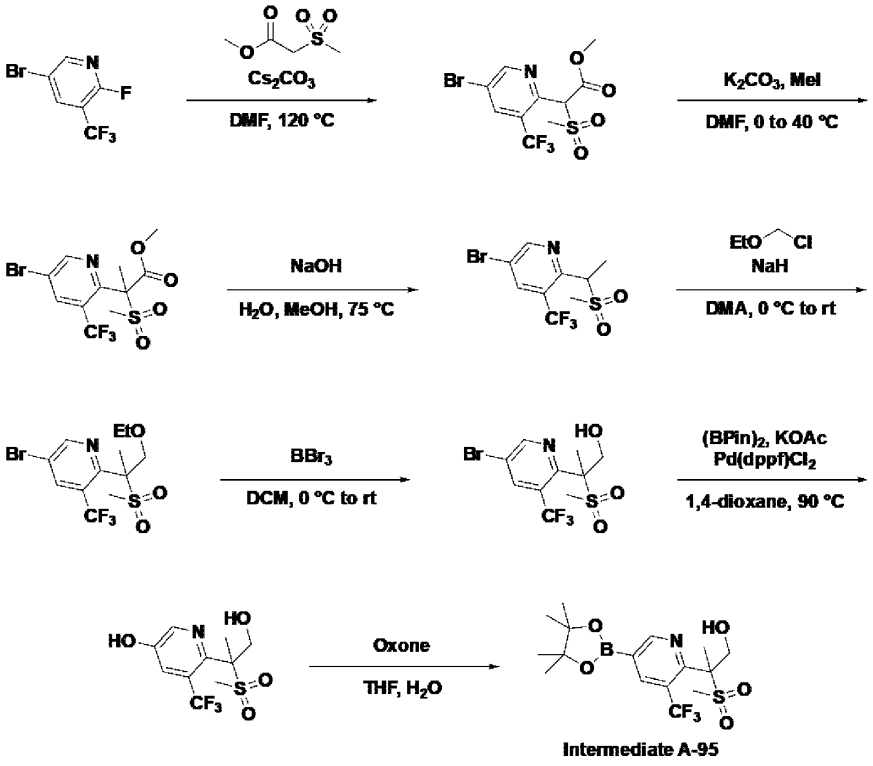
[0852] A mixture of (*cis*)-3-[5-bromo-7-(trifluoromethyl)-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol (6.00 g, 17.2 mmol), 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5,5-dimethyl-1,3,2-dioxaborinane (5.82 g, 25.8 mmol), KOAc (5.06 g, 51.6 mmol) and $Pd(dppf)Cl_2$ (130 mg, 0.172 mmol) in 1,4-dioxane (60 mL) was purged with N_2 (3x) and then stirred at 100 °C for 16 h. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated in vacuo to give (*cis*)-3-[5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-7-(trifluoromethyl)-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol, which was used in the subsequent step without further purification.

Step 6: 1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-ol

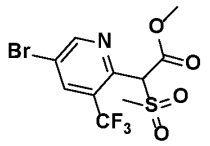


[0853] To a 0 °C solution of (*cis*)-3-[5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-7-(trifluoromethyl)-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol (9.00 g, 23.6 mmol) in THF (50 mL) and H_2O (50 mL) was added Oxone (14.5 g, 23.6 mmol). The mixture was stirred at room temperature for 2 h. The mixture was cooled to 0 °C and quenched by addition of saturated aqueous Na_2SO_3 (60 mL). The mixture was adjusted to pH = 7 by addition of saturated aqueous $NaHCO_3$ and extracted with EtOAc (2 x 60 mL). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was triturated with MTBE (20 mL) to give 1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-ol (**Intermediate A-92**), which was used in the subsequent step without further purification. MS = 287.1 $[M+H]^+$.

General Procedure for Intermediates A-93 & A-94

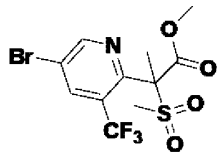


Step 1: methyl 2-[5-bromo-3-(trifluoromethyl)pyridin-2-yl]-2-methanesulfonylacetate



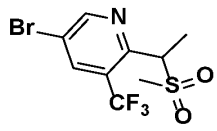
[0854] To a solution of 5-bromo-2-chloro-3-(trifluoromethyl)pyridine (7.50 g, 28.8 mmol) in DMF (70 mL) was added Cs_2CO_3 (23.5 g, 72.0 mmol) and methyl 2-methylsulfonylacetate (6.57 g, 43.2 mmol). The mixture was stirred at 120 °C for 2 h. After cooling to 0 °C, the reaction mixture was quenched by addition of H_2O (70 mL), and then extracted with EtOAc (5 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 220 g cartridge, 0–20% EtOAc/Petroleum ether) to give methyl 2-[5-bromo-3-(trifluoromethyl)pyridin-2-yl]-2-methanesulfonylacetate. MS = 376.1 / 378.0 $[M+H]^+$.

Step 2: methyl 2-[5-bromo-3-(trifluoromethyl)pyridin-2-yl]-2-methanesulfonylpropanoate



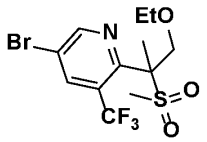
[0855] To a 0 °C solution of methyl 2-[5-bromo-3-(trifluoromethyl)pyridin-2-yl]-2-methanesulfonylacetate (14.0 g, 37.2 mmol) and K_2CO_3 (10.3 g, 74.4 mmol) in DMF (140 mL) was added MeI (10.6 g, 74.4 mmol) dropwise via syringe. The mixture was stirred at 40 °C for 4 h. The reaction mixture was quenched by addition of ice water (100 mL) and stirred below 10 °C for 10 min, and then extracted with EtOAc (3 x 150 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 220 g cartridge, 0–30% EtOAc/Petroleum ether) to give methyl 2-[5-bromo-3-(trifluoromethyl)pyridin-2-yl]-2-methanesulfonylpropanoate. MS = 390.1 / 392.1 $[M+H]^+$.

Step 3: 5-bromo-2-(1-methanesulfonylethyl)-3-(trifluoromethyl)pyridine



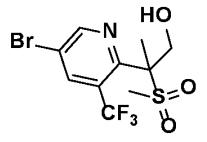
[0856] To a solution of methyl 2-[5-bromo-3-(trifluoromethyl)pyridin-2-yl]-2-methanesulfonylpropanoate (13.0 g, 33.3 mmol) in H_2O (20 mL) and MeOH (50 mL) was added a solution of NaOH (13.3 g, 333 mmol) in H_2O (30 mL). The mixture was stirred at 75 °C for 6 h. After cooling to room temperature, the reaction mixture was filtered, and the filter cake was washed with H_2O (3 x 30 mL). The filter cake was dried in vacuo to give 5-bromo-2-(1-methanesulfonylethyl)-3-(trifluoromethyl)pyridine, which was taken to the next step without further purification MS = 332.1 / 334.1 $[M+H]^+$.

Step 4: 5-bromo-2-(1-ethoxy-2-methanesulfonylpropan-2-yl)-3-(trifluoromethyl)pyridine



[0857] To a round-bottom flask equipped with a magnetic stir bar and thermometer under N_2 atmosphere was added 5-bromo-2-(1-methanesulfonylethyl)-3-(trifluoromethyl)pyridine (7.20 g, 21.7 mmol) and DMA (420 mL). The mixture was cooled to 0 °C and NaH (3.48 g, 86.7 mmol, 60% in mineral oil) was added slowly. The resulting mixture was stirred for 3 h at room temperature under N_2 atmosphere. Chloromethoxyethane (10.26 g, 108 mmol) was then slowly added to the reaction mixture. The reaction mixture was stirred at room temperature for 2 h, then was cooled to 10 °C and quenched by addition of saturated aqueous NH_4Cl solution (150 mL). The mixture was extracted with EtOAc (3 x 100 mL), then the combined organic layers were washed with brine (150 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 80 g cartridge, 0–25% EtOAc/Petroleum ether) to give 5-bromo-2-(1-ethoxy-2-methanesulfonylpropan-2-yl)-3-(trifluoromethyl)pyridine. MS = 389.9 / 391.9 $[M+H]^+$.

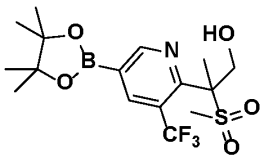
Step 5: 2-[5-bromo-3-(trifluoromethyl)pyridin-2-yl]-2-methanesulfonylpropan-1-ol



[0858] To a round-bottom flask equipped with a magnetic stir bar and thermometer were added 5-bromo-2-(1-ethoxy-2-methanesulfonylpropan-2-yl)-3-(trifluoromethyl)pyridine (3.90 g, 9.99 mmol) and DCM (150 mL). The mixture was cooled to 0 °C and BBr_3 (12.5 g, 50.0 mmol) was

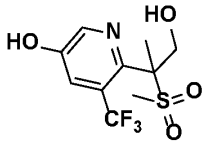
added dropwise via syringe. The resulting mixture was stirred for 6 h at room temperature. The reaction mixture was then cooled to 10 °C and quenched by addition of saturated aqueous $NaHCO_3$ solution (150 mL) and then extracted with EtOAc (3 x 75 mL). The combined organic layers were washed with brine (150 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 40 g cartridge, 0–25% EtOAc/Petroleum ether) to give 2-[5-bromo-3-(trifluoromethyl)605pyridine-2-yl]-2-methanesulfonylpropan-1-ol. MS = 361.9 / 363.9 $[M+H]^+$.

Step 6: 2-methanesulfonyl-2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridine-2-yl]propan-1-ol



[0859] A mixture of 2-[5-bromo-3-(trifluoromethyl)pyridine-2-yl]-2-methanesulfonylpropan-1-ol (1.20 g, 3.31 mmol), bis(pinacolato)diboron (1.01 g, 3.98 mmol), KOAc (650 mg, 6.63 mmol), and $Pd(dppf)Cl_2$ (242 mg, 331 μmol) in 1,4-dioxane (16 mL) was degassed and purged with N_2 (3x). The mixture was then stirred at 90 °C for 16 h under N_2 atmosphere. After cooling to room temperature, the mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo to give 2-methanesulfonyl-2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridin-2-yl]propan-1-ol, which was taken to the next step without further purification. MS = 328.1 $[M - C_6H_{10}+H]^+$.

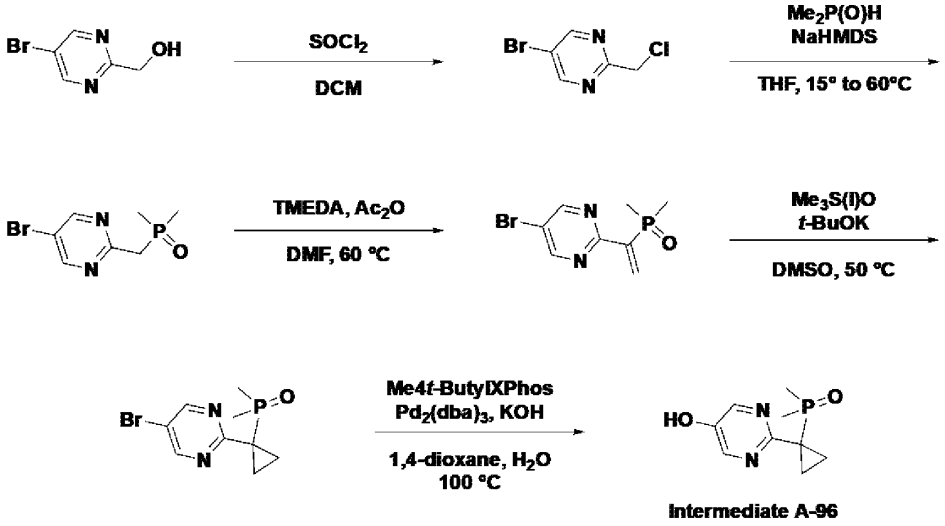
Step 7: 6-(1-hydroxy-2-methanesulfonylpropan-2-yl)-5-(trifluoromethyl)pyridin-3-ol



[0860] To a solution of 2-methanesulfonyl-2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridin-2-yl]propan-1-ol (2.00 g, 4.88 mmol) in acetone (15 mL) and H_2O (15 mL) was added Oxone (6.00 g, 9.78 mmol). The mixture was stirred at room temperature for 2 h. The reaction mixture was cooled to 0 °C, quenched by addition of saturated aqueous Na_2SO_3 solution

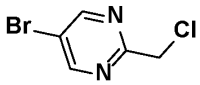
(50 mL), then stirred for 30 min. The mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–50% EtOAc/Petroleum ether) to give 6-(1-hydroxy-2-methanesulfonylpropan-2-yl)-5-(trifluoromethyl)pyridin-3-ol (**Intermediate A-95**). MS = 300.0 $[M+H]^+$.

General Procedure for Intermediate A-96



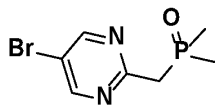
Intermediate A-96

Step 1: 5-bromo-2-(chloromethyl)pyrimidine



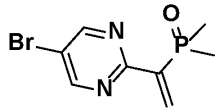
[0861] To a solution of (5-bromopyrimidin-2-yl)methanol (4.00 g, 21.2 mmol) in DCM (200 mL) was added $SOCl_2$ (20 mL) slowly via syringe. The mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was quenched with H_2O (80 mL). The mixture was adjusted to pH = 8 with saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give 5-bromo-2-(chloromethyl)pyrimidine, which was taken to the next step without further purification. ^1H NMR (400 MHz, DMSO-d_6): δ 9.05 (s, 2H), 4.81 (s, 2H).

Step 2: 5-bromo-2-[(dimethylphosphoryl)methyl]pyrimidine



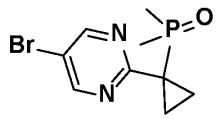
[0862] To a 250 mL three-necked round bottom flask equipped with magnetic stirrer, addition funnel, and thermometer under N_2 atmosphere were added dimethylphosphine oxide (1.66 g, 21.2 mmol) and THF (140 mL). To the mixture was added 1 M NaHMDS in THF (23.1 mL, 23.1 mmol) portionwise while keeping the temperature of the reaction mixture between 15–20 °C. The mixture was stirred at 15 °C for 1 h under N_2, and then a solution of 5-bromo-2-(chloromethyl)pyrimidine (4.00 g, 19.3 mmol) in THF (30 mL) was added dropwise. The resulting mixture was heated to 60 °C and stirred for 15 h under N_2 atmosphere. The reaction mixture was cooled to 10 °C and quenched by addition of saturated NH_4Cl solution (100 mL) and stirred for 10 min, and then extracted with EtOAc (3 x 80 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by reverse phase preparative HPLC (Welch Xtimate C_{18} column, 0–20% MeCN:10 mM NH_4HCO_3 in H_2O) to give 5-bromo-2-[(dimethylphosphoryl)methyl]pyrimidine. MS = 248.9 / 250.9 $[M+H]^+$.

Step 3: 5-bromo-2-[1-(dimethylphosphoryl)ethenyl]pyrimidine



[0863] To a solution of 5-bromo-2-(dimethylphosphorylmethyl)pyrimidine (1.00 g, 4.02 mmol) and *N,N,N′,N′*-tetramethylmethanediamine (821 mg, 8.03 mmol) in DMF (8 mL) was added Ac_2O (1.64 g, 16.1 mmol). The mixture was stirred at 60 °C for 2 h. After cooling to room temperature, the reaction was filtered. The residue was purified by reverse phase preparative HPLC (Phenomenex Luna C_{18} column, 5–35% MeCN:10 mM TFA in H_2O) to give 5-bromo-2-[1-(dimethylphosphoryl)ethenyl]pyrimidine. MS = 260.9 / 262.9 $[M+H]^+$.

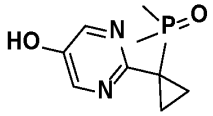
Step 4: 5-bromo-2-[1-(dimethylphosphoryl)cyclopropyl]pyrimidine



[0864] To a solution of trimethylsulfoxonium iodide (2.02 g, 9.19 mmol) in DMSO (6 mL) was added *t*-BuOK (904 mg, 8.04 mmol). The mixture was stirred at 50 °C for 30 min, and then a

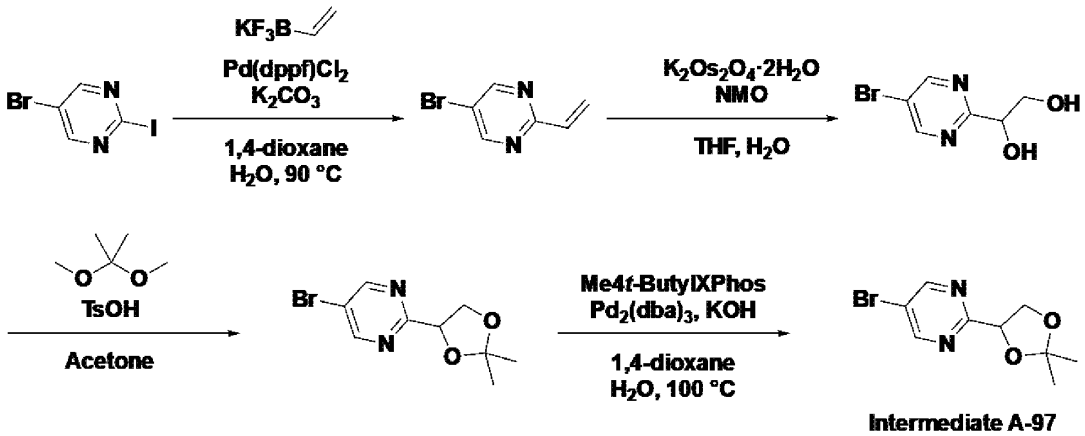
solution of 5-bromo-2-[1-(dimethylphosphoryl)ethenyl]pyrimidine (600 mg, 2.30 mmol) in DMSO (1 mL) was added dropwise. The mixture was stirred at 50 °C for 30 min. After cooling to room temperature, the reaction was filtered, and the filtrate was concentrated in vacuo. The residue was purified by reverse phase preparative HPLC (Phenomenex Luna C_{18} column, 1–40% MeCN:10 mM TFA in H_2O) to give 5-bromo-2-[1-(dimethylphosphoryl)cyclopropyl]pyrimidine. MS = 274.9 / 276.9 $[M+H]^+$.

Step 5: 2-[1-(dimethylphosphoryl)cyclopropyl]pyrimidin-5-ol

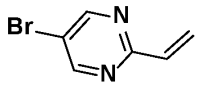


[0865] A mixture of 5-bromo-2-[1-(dimethylphosphoryl)cyclopropyl]pyrimidine (400 mg, 1.45 mmol), di-tert-butyl-[2,3,4,5-tetramethyl-6-(2,4,6-triisopropylphenyl)phenyl]phosphane (69.9 mg, 145 μmol), $Pd_2(dba)_3$ (26.6 mg, 29.1 μmol) and KOH (245 mg, 4.36 mmol) in 1,4-dioxane (5 mL) and H_2O (2 mL) was degassed and purged with N_2 (3x). The mixture was stirred at 100 °C for 16 h under N_2 atmosphere. After cooling to room temperature, the reaction mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified by reverse phase preparative HPLC (Phenomenex Luna C_{18} column, 1–25% MeCN:10 mM TFA in H_2O) to give 2-[1-(dimethylphosphoryl)cyclopropyl]pyrimidin-5-ol (**Intermediate A-96**). MS = 213.2 $[M+H]^+$.

General Procedure for Intermediate A-97

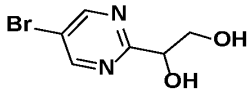


Step 1：5-bromo-2-vinylpyrimidine



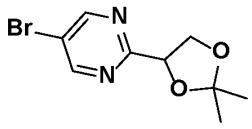
[0866] A mixture of 5-bromo-2-iodo-pyrimidine (5.00 g, 17.6 mmol), potassium vinyltrifluoroborate (2.59 g, 19.3 mmol), $Pd(dppf)Cl_2$ (1.28 g, 1.76 mmol), and K_2CO_3 (6.06 g, 43.9 mmol) in 1,4-dioxane (75 mL) and H_2O (25 mL) was degassed and purged with N_2 (3x). The mixture was stirred at 90 °C for 12 h under N_2 atmosphere. After cooling to room temperature, the reaction mixture was diluted with H_2O (60 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 40 g cartridge, 0–15% EtOAc/Petroleum ether) to give 5-bromo-2-vinyl-pyrimidine. MS = 185.1 / 187.1 $[M+H]^+$.

Step 2: 1-(5-bromopyrimidin-2-yl)ethane-1,2-diol



[0867] To a 0 °C solution of 5-bromo-2-vinyl-pyrimidine (1.80 g, 9.73 mmol) in THF (20 mL) and H_2O (20 mL) was added $K_2OsO_4 \cdot 2H_2O$ (358 mg, 97 μmol) and NMO (2.28 g, 19.5 mmol). The mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by reverse phase preparative HPLC (Welch Xtimate C_{18} column, 0–20% MeCN:10 mM NH_4HCO_3 in H_2O) to give 1-(5-bromopyrimidin-2-yl)ethane-1,2-diol. MS = 219.1 / 221.1 $[M+H]^+$.

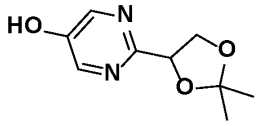
Step 3: 5-bromo-2-(2,2-dimethyl-1,3-dioxolan-4-yl)pyrimidine



[0868] To a solution of 1-(5-bromopyrimidin-2-yl)ethane-1,2-diol (860 mg, 3.93 mmol) in acetone (9 mL) was added 2,2-dimethoxypropane (8.18 g, 78.5 mmol) and TsOH (67.6 mg, 0.393 mmol). The mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (4 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel

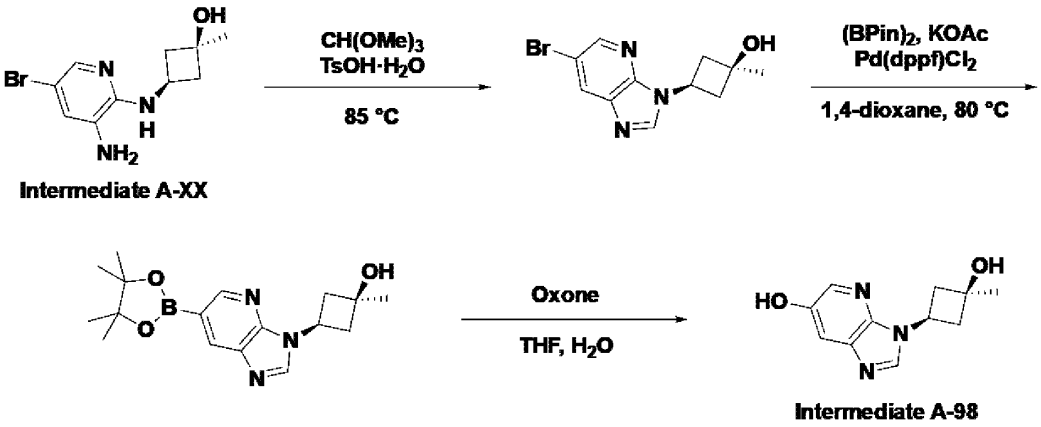
chromatography (Biotage 12 g cartridge, 0–70% EtOAc/Petroleum ether) to give 5-bromo-2-(2,2-dimethyl-1,3-dioxolan-4-yl)pyrimidine. MS = 259.0 / 261.0 $[M+H]^+$.

Step 4: 2-(2,2-dimethyl-1,3-dioxolan-4-yl)pyrimidin-5-ol



[0869] A mixture of 5-bromo-2-(2,2-dimethyl-1,3-dioxolan-4-yl)pyrimidine (200 mg, 0.772 mmol), $Pd_2(dba)_3$ (14.0 mg, 15.4 μmol), di-*tert*-butyl-[2,3,4,5-tetramethyl-6-(2,4,6-triisopropylphenyl)phenyl]phosphane (37.0 mg, 77.2 μmol) and KOH (130 mg, 2.32 mmol) in H_2O (2 mL) and 1,4-dioxane (5 mL) was degassed and purged with N_2 (3x). The mixture was stirred at 100 °C for 16 h under N_2 atmosphere. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated in vacuo to give 2-(2,2-dimethyl-1,3-dioxolan-4-yl)pyrimidin-5-ol (**Intermediate A-97**), which was taken to the next step without further purification. MS = 197.1 $[M+H]^+$.

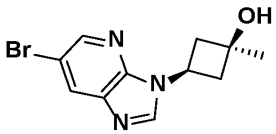
General Procedure for Intermediate A-98



Intermediate A-XX

Intermediate A-98

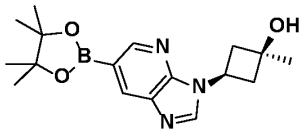
Step 1: (*cis*)-3-{6-bromo-3H-imidazo[4,5-b]pyridine-3-yl}-1-methylcyclobutan-1-ol



[0870] To a solution of (*cis*)-3-[(3-amino-5-bromopyridin-2-yl)amino]-1-methylcyclobutan-1-ol (**Intermediate A-93**, 750 mg, 2.76 mmol) in $CH(OMe)_3$ (10 mL) was added $TsOH•H_2O$ (52.4 mg,

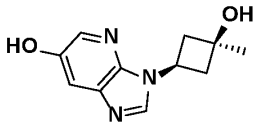
0.276 mmol). The mixture was stirred at 85 °C for 2 h. After cooling to room temperature, the mixture was diluted with H_2O (30 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give (*cis*)-3-{6-bromo-3H-imidazo[4,5-b]pyridin-3-yl}-1-methylcyclobutan-1-ol, which was taken to the next step without further purification. MS = 282.0 / 284.0 $[M+H]^+$.

Step 2: (*cis*)-1-methyl-3-[6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl]cyclobutan-1-ol



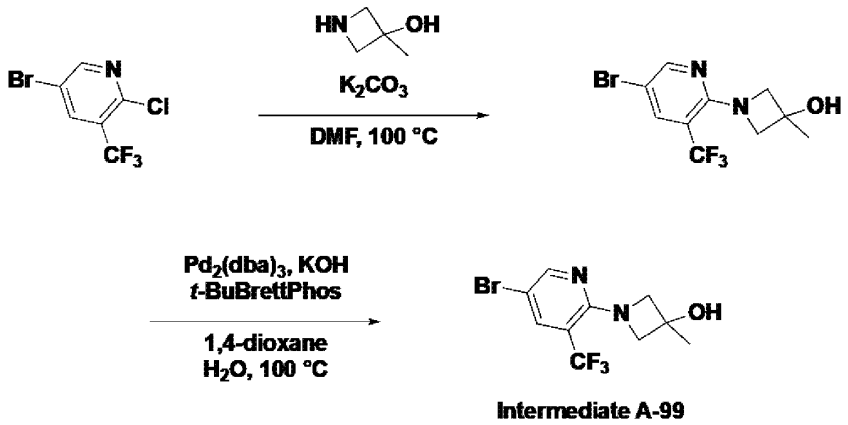
[0871] To a solution of (*cis*)-3-{6-bromo-3H-imidazo[4,5-b]pyridin-3-yl}-1-methylcyclobutan-1-ol (500 mg, 1.77 mmol) in 1,4-dioxane (4 mL) were added bis(pinacolato)diboron (540 mg, 2.13 mmol), KOAc (348 mg, 3.54 mmol) and $Pd(dppf)Cl_2$ (130 mg, 177 µmol). The mixture was degassed and purged with N_2 (3x), then stirred at 80 °C for 16 h under N_2 atmosphere. After cooling to room temperature, the mixture was filtered and concentrated in vacuo to give (*cis*)-1-methyl-3-[6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl]cyclobutan-1-ol, which was taken to the next step without further purification. MS = 247.9 $[M–C_6H_{10}+H]^+$.

Step 3: 3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-3H-imidazo[4,5-b]pyridin-6-ol



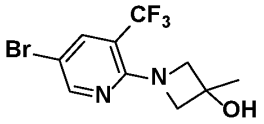
[0872] To a solution of (*cis*)-1-methyl-3-[6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl]cyclobutan-1-ol (300 mg, 0.911 mmol) in THF (2 mL) and H_2O (2 mL) was added Oxone (560 mg, 911 µmol). The mixture was stirred at room temperature for 2 h. The mixture was concentrated in vacuo to give 3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-3H-imidazo[4,5-b]pyridin-6-ol (**Intermediate A-98**), which was taken to the next step without further purification. MS = 220.2 $[M+H]^+$.

General Procedure for Intermediate A-99



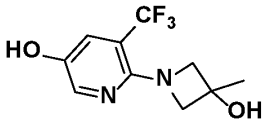
Intermediate A-99

Step 1: 1-[5-bromo-3-(trifluoromethyl)pyridin-2-yl]-3-methylazetidin-3-ol



[0873] To a solution of 5-bromo-2-chloro-3-(trifluoromethyl)pyridine (1.00 g, 3.84 mmol) and 3-methylazetidin-3-ol (522 mg, 4.22 mmol, HCl salt) in DMF (10 mL) was added K_2CO_3 (1.86 g, 13.4 mmol). The mixture was stirred at 100 °C for 16 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo. The residue was diluted with H_2O (20 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–50% EtOAc/Petroleum ether) to give 1-[5-bromo-3-(trifluoromethyl)pyridin-2-yl]-3-methylazetidin-3-ol. MS = 311.0 / 313.0 $[M+H]^+$.

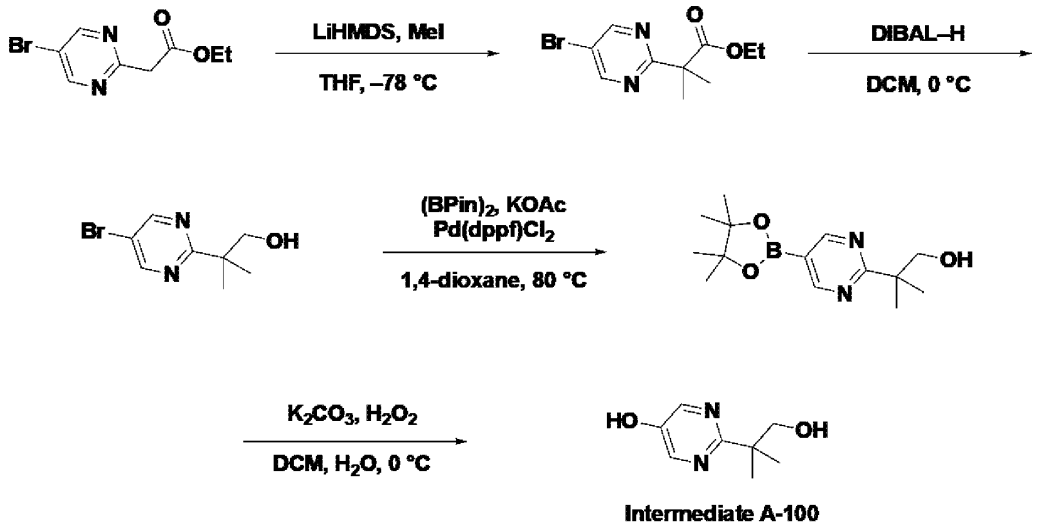
Step 2: 6-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyridin-3-ol



[0874] A mixture of 1-[5-bromo-3-(trifluoromethyl)pyridin-2-yl]-3-methylazetidin-3-ol (900 mg, 2.89 mmol), $Pd_2(dba)_3$ (53.0 mg, 57.9 μmol), *t*-BuBrettphos (1.40 g, 2.89 mmol) and KOH (487 mg, 8.68 mmol) in 1,4-dioxane (15 mL) and H_2O (6 mL) was degassed and purged with N_2 (3x). The mixture was stirred at 100 °C for 16 h under N_2 atmosphere. The reaction mixture was allowed to cool to room temperature, then was concentrated in vacuo. The residue was purified by flash

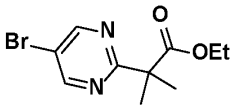
silica gel chromatography (Biotage 12 g cartridge, 0–100% EtOAc/Petroleum ether) to give 6-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyridin-3-ol (**Intermediate A-99**). MS = 249.2 $[M+H]^+$.

General Procedure for Intermediate A-100



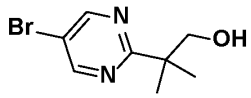
Intermediate A-100

Step 1: ethyl 2-(5-bromopyrimidin-2-yl)-2-methylpropanoate



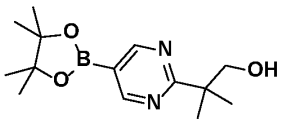
[0875] To a three-neck round-bottom flask equipped with a magnetic stir bar and thermometer under N_2 atmosphere was added ethyl 2-(5-bromopyrimidin-2-yl)acetate (2.00 g, 8.16 mmol) and THF (20 mL). The mixture was cooled to –78 °C and 1.0 M LiHMDS in THF (8.98 mL, 8.98 mmol) was added dropwise. After stirring at –78 °C for 1 h, MeI (2.42 g, 17.1 mmol) was added in one portion. The mixture was warmed up to room temperature and stirred for 2 h under N_2 atmosphere. The reaction mixture was cooled to ~0–5°C and quenched by addition of saturated aqueous NH_4Cl (40 mL), then diluted with H_2O (20 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (2 x 25 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give ethyl 2-(5-bromopyrimidin-2-yl)-2-methylpropanoate, which was taken to the next step without further purification. MS = 273.2 / 275.2 $[M+H]^+$.

Step 2: 2-(5-bromopyrimidin-2-yl)-2-methylpropan-1-ol



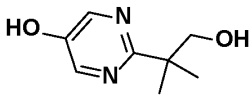
[0876] To a three-neck round-bottom flask equipped with a magnetic stir bar and thermometer under N_2 atmosphere were added ethyl 2-(5-bromopyrimidin-2-yl)-2-methylpropanoate (2.60 g, 9.52 mmol) and DCM (30 mL). The mixture was cooled to 0 °C and 1.0 M DIBAL-H in THF (19.0 mL, 19.0 mmol) was added dropwise. The mixture was stirred at 0 °C for 3 h under N_2 atmosphere. The reaction mixture was quenched by addition of H_2O (60 mL), adjusted to pH = 3–4 by dropwise addition of aqueous 3.0 M HCl, then extracted with DCM (3 x 30 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 20 g cartridge, 20–60% EtOAc /Petroleum ether) to give 2-(5-bromopyrimidin-2-yl)-2-methylpropan-1-ol. MS = 231.0 / 233.0 $[M+H]^+$.

Step 3: 2-methyl-2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl]propan-1-ol



[0877] A mixture of 2-(5-bromopyrimidin-2-yl)-2-methylpropan-1-ol (800 mg, 3.46 mmol), bis(pinacolato)diboron (1.32 g, 5.19 mmol), KOAc (1.02 g, 10.4 mmol) and $Pd(dppf)Cl_2$ (253 mg, 346 μmol) in 1,4-dioxane (10 mL) was degassed and purged with N_2 (3x), and then the mixture was stirred at 80 °C for 16 h under N_2 atmosphere. After cooling to room temperature, the mixture was filtered, the filtrate was concentrated in vacuo to give 2-methyl-2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl]propan-1-ol, which was taken to the next step without further purification. MS = 197.2 $[M - C_6H_{10}+H]^+$.

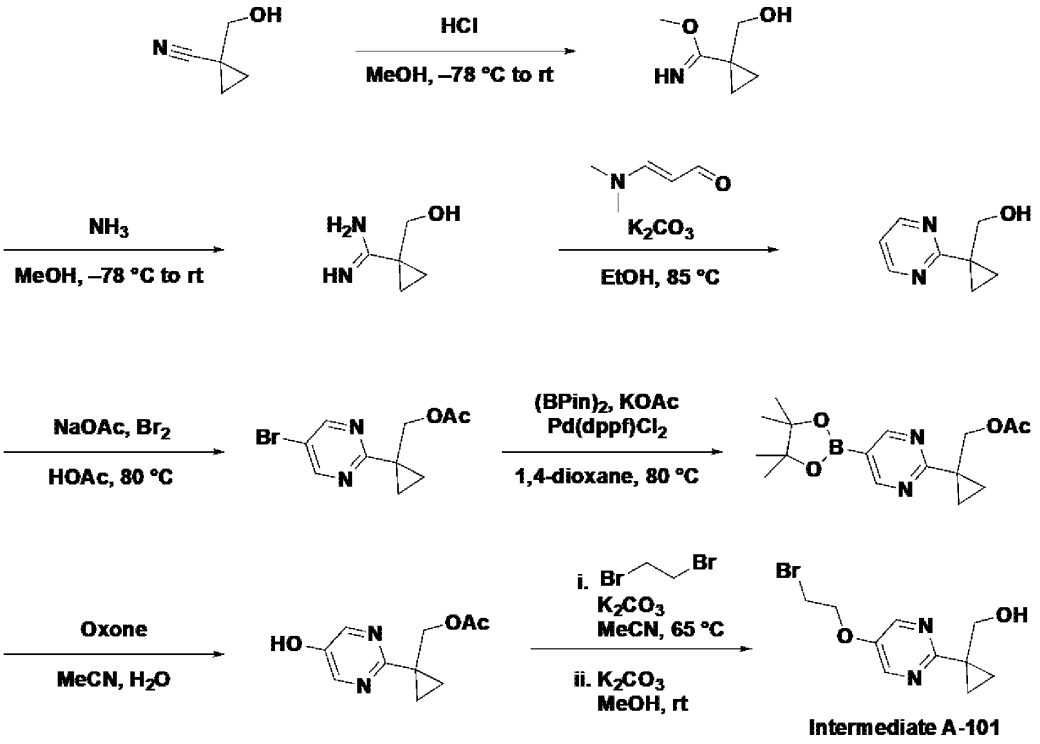
Step 4: 2-(1-hydroxy-2-methylpropan-2-yl)pyrimidin-5-ol



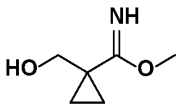
[0878] To a three-neck round-bottom flask equipped with a magnetic stir bar and thermometer under a N_2 atmosphere were added 2-methyl-2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl]propan-1-ol (960 mg, 3.45 mmol), K_2CO_3 (1.19 g, 8.63 mmol) and DCM (10

mL). The mixture was cooled to 0 °C and 30% H_2O_2 in H_2O (1.16 mL, 12.1 mmol) was added in portions. The mixture was stirred at 0 °C for 2 h under N_2 atmosphere. The reaction mixture was quenched by addition of saturated aqueous Na_2SO_3 solution (20 mL), and then the reaction mixture was concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters Xbridge OBD C_{18} column, 20% MeCN:10 mM NH_4HCO_3 in H_2O) to give 2-(1-hydroxy-2-methylpropan-2-yl)pyrimidin-5-ol (**Intermediate A-100**). MS = 169.2 $[M+H]^+$.

General Procedure for Intermediate A-101



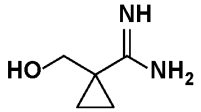
Step 1: methyl 1-(hydroxymethyl)cyclopropanecarboximidate



[0879] HCl gas was bubbled into a solution of 1-(hydroxymethyl)cyclopropanecarbonitrile (4.00 g, 41.2 mmol) in MeOH (40 mL) at –78 °C for 20 min. The mixture was then stirred at room temperature for 15 h. The mixture was concentrated in vacuo to give methyl 1-

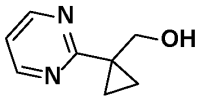
(hydroxymethyl)cyclopropanecarboximidate, which was taken to the next step without further purification. MS= 130.0 $[M+H]^+$.

Step 2: 1-(hydroxymethyl)cyclopropanecarboxamidine



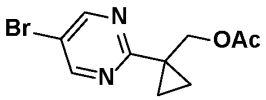
[0880] NH_3 gas was bubbled into a solution of methyl 1-(hydroxymethyl)cyclopropanecarboximidate (6.00 g, 46.5 mmol) in MeOH (60 mL) at –78 °C for 10 min. The mixture was then stirred at room temperature for 15 h. The mixture was concentrated in vacuo to give 1-(hydroxymethyl)cyclopropanecarboxamidine, which was taken to the next step without further purification. MS = 115.2 $[M+H]^+$.

Step 3: [1-(pyrimidin-2-yl)cyclopropyl]methanol



[0881] A mixture of 1-(hydroxymethyl)cyclopropanecarboxamidine (5.50 g, 48.2 mmol), (*E*)-3-(dimethylamino)prop-2-enal (4.54 g, 45.8 mmol) and K_2CO_3 (13.3 g, 96.4 mmol) in EtOH (50 mL) was stirred at 85 °C for 15 h. The mixture was concentrated in vacuo. The residue was diluted with water (60 mL) at 0 °C, and then extracted with EtOAc (4 x 20 mL). The combined organic layers were washed with brine (50 mL x 2), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 40 g cartridge, 0–50% EtOAc/Petroleum ether) to give [1-(pyrimidin-2-yl)cyclopropyl]methanol. MS= 151.2 $[M+H]^+$.

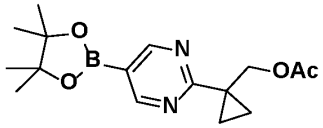
Step 4: [1-(5-bromopyrimidin-2-yl)cyclopropyl]methyl acetate



[0882] To a solution of (1-pyrimidin-2-ylcyclopropyl)methanol (1.00 g, 6.66 mmol) in HOAc (10 mL) was added NaOAc (655 mg, 7.99 mmol). The mixture was heated to 80 °C, Br_2 (1.60 g, 9.99 mmol) was added, and the reaction was stirred at 80 °C for 3 h. After cooling to 0 °C, the reaction mixture was quenched by addition of H_2O (20 mL). The mixture was adjusted to pH = 8 by slow addition of solid NaOH, and then extracted with EtOAc (3 x 15 mL). The combined organic

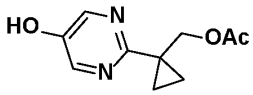
layers were washed with brine (2 x 30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–20% EtOAc/Petroleum ether) to give [1-(5-bromopyrimidin-2-yl)cyclopropyl]methyl acetate. MS = 271.0 / 272.9 $[M+H]^+$.

Step 5: {1-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl]cyclopropyl}methyl acetate



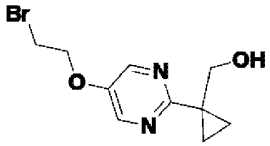
[0883] A mixture of [1-(5-bromopyrimidin-2-yl)cyclopropyl]methyl acetate (500 mg, 1.84 mmol), bis(pinacolato)diboron (609 mg, 2.40 mmol), KOAc (543 mg, 5.53 mmol), and $Pd(dppf)Cl_2$ (67.5 mg, 92.2 μmol) in 1,4-dioxane (15 mL) was degassed and purged with (N_2 3x), and then the mixture was stirred at 80 °C for 15 h under N_2 atmosphere. The mixture was filtered, and the filtrate was concentrated in vacuo to give {1-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl]cyclopropyl}methyl acetate, which was taken to the next step without further purification. MS= 319.3 $[M+H]^+$.

Step 6: [1-(5-hydroxypyrimidin-2-yl)cyclopropyl]methyl acetate



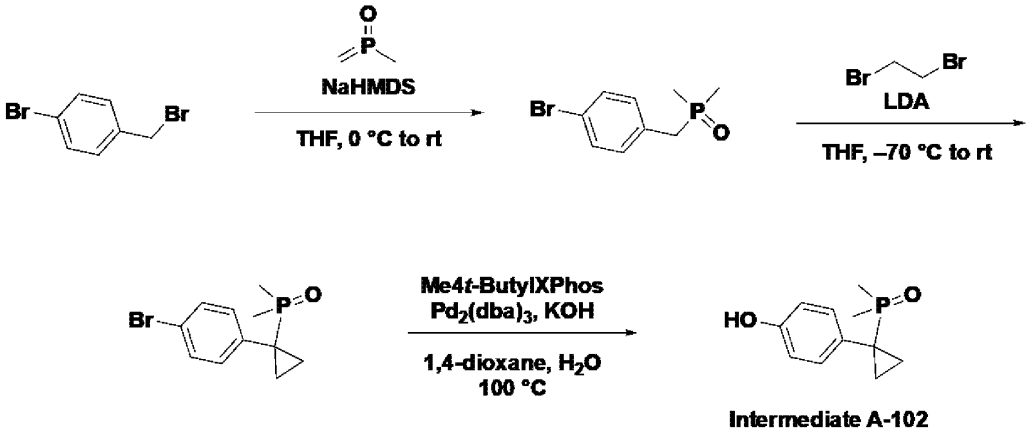
[0884] To a solution of {1-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl]cyclopropyl}methyl acetate (800 mg, 2.51 mmol) in MeCN (10 mL) and H_2O (10 mL) was added Oxone (1.85 g, 3.01 mmol). The mixture was stirred at room temperature for 2 h. After cooling to 0 °C, the reaction mixture was quenched by addition of saturated aqueous Na_2SO_3 solution (15 mL), and then extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–50% EtOAc/Petroleum ether) to give [1-(5-hydroxypyrimidin-2-yl)cyclopropyl]methyl acetate MS = 209.2 $[M+H]^+$.

Step 7: {1-[5-(2-bromoethoxy)pyrimidin-2-yl]cyclopropyl}methanol

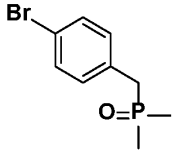


[0885] To a solution of [1-(5-hydroxypyrimidin-2-yl)cyclopropyl]methyl acetate (400 mg, 1.92 mmol) in MeCN (5 mL) was added K_2CO_3 (1.06 g, 7.68 mmol) and 1,2-dibromoethane (5.79 mL, 76.8 mmol). The mixture was stirred at 65°C for 15 h. The mixture was cooled to room temperature and MeOH (10 mL) and additional K_2CO_3 (1.06 g, 7.68 mmol) was added, and the reaction was stirred for 2 h. The mixture was filtered, and the filtrate was concentrated to provide [{1-[5-(2-bromoethoxy)pyrimidin-2-yl]cyclopropyl}methanol (**Intermediate 101**), which was used in the subsequent step without further purification. MS = 273.2 / 275.1 $[M+H]^+$.

General Procedure for Intermediate A-102



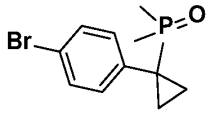
Step 1: 1-bromo-4-[(dimethylphosphoryl)methyl]benzene



[0886] In a three-neck round-bottom flask with a magnetic stir bar and thermometer, 1.0 M NaHMDS in THF (96.0 mL, 96.0 mmol) was added dropwise to a 0 °C solution of methylphosphonoylmethane (6.87 g, 88.2 mmol) in THF (200 mL). The mixture was stirred at 0 °C for 15 min, and then a solution of 1-bromo-4-(bromomethyl)benzene (20.0 g, 80.0 mmol) in THF (25 mL) was added dropwise. The resulting mixture was stirred at room temperature for 2 h. The

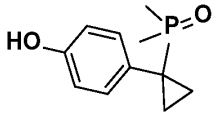
mixture was quenched with H_2O (200 mL) and extracted with DCM (5 x 50 mL). The combined organic layers were dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo. The residue was purified by flash silica gel chromatography (Biotage 80 g cartridge, 0–10% MeOH/EtOAc) to give 1-bromo-4-[(dimethylphosphoryl)methyl]benzene. MS = 247.0 / 249.0 $[M+H]^+$.

Step 2: 1-bromo-4-[1-(dimethylphosphoryl)cyclopropyl]benzene



[0887] To a three-necked round-bottom flask equipped with a magnetic stir bar and thermometer under N_2 atmosphere were added 1-bromo-4-(dimethylphosphorylmethyl)benzene (3.00 g, 12.1 mmol) and freshly distilled THF (40 mL). The mixture was cooled to –70 °C and 2.0 M LDA in THF (13.4 mL, 13.4 mmol) was added dropwise. The mixture was stirred for 10 min at –70 °C, then 1,2-dibromoethane (3.42 g, 18.1 mmol) was added, and the mixture was stirred at room temperature for 6 h. The reaction was cooled to 0 °C, quenched with H_2O (15 mL), and then stirred at 0 °C for 10 min. The mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex Luna C_{18} column, 25–55% MeCN:10 mM TFA in H_2O) to give 1-bromo-4-[1-(dimethylphosphoryl)cyclopropyl]benzene. MS = 273.1 / 275.1 $[M+H]^+$.

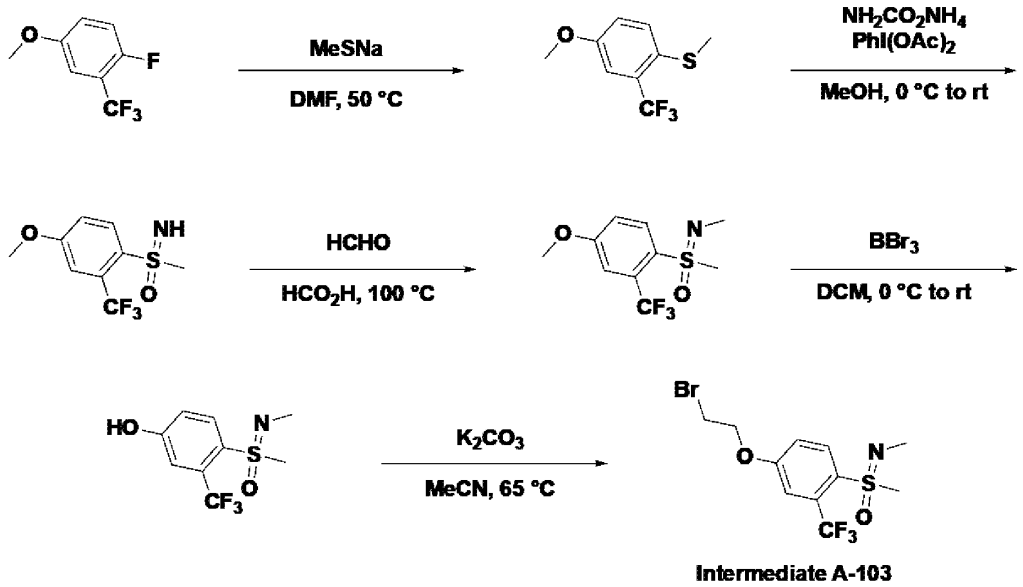
Step 3: 4-[1-(dimethylphosphoryl)cyclopropyl]phenol



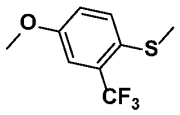
[0888] A mixture of 1-bromo-4-(1-dimethylphosphorylcyclopropyl)benzene (350 mg, 1.28 mmol), ditert-butyl-[2,3,4,5-tetramethyl-6-(2,4,6-triisopropylphenyl)phenyl]phosphane (61.6 mg, 128 µmol), $Pd_2(dba)_3$ (23.5 mg, 25.6 µmol) and KOH (216 mg, 3.84 mmol) in 1,4-dioxane (5 mL) and H_2O (2 mL) was degassed and purged with N_2 (3x). The mixture was stirred at 100 °C for 16 h. After cooling to room temperature, the reaction mixture was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC

(Phenomenex Luna C_{18} column, 1–45% MeCN:10 mM TFA in H_2O) to give 4-[1-(dimethylphosphoryl)cyclopropyl]phenol (Intermediate A-102). MS = 211.0 $[M+H]^+$.

General Procedure for Intermediate A-103

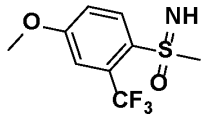


Step 1: 4-methoxy-1-(methylsulfanyl)-2-(trifluoromethyl)benzene



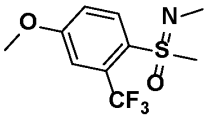
[0889] A mixture of 1-fluoro-4-methoxy-2-(trifluoromethyl)benzene (10.0 g, 51.5 mmol) and sodium methanethiolate (5.42 g, 77.3 mmol) in DMF (100 mL) was stirred at 50 °C for 16 h. After cooling to 0 °C, the reaction mixture was quenched by addition of H_2O (150 mL) and then extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with H_2O (3 x 150 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 4-methoxy-1-(methylsulfanyl)-2-(trifluoromethyl)benzene, which was taken to the next step without further purification. ^1H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, J = 8.4 Hz, 1H), 7.20 (d, J = 2.8 Hz, 1H), 7.03 (dd, J = 8.4, 2.4 Hz, 1H), 3.84 (s, 3H), 2.46 (s, 3H).

Step 2: imino[4-methoxy-2-(trifluoromethyl)phenyl]methyl-λ⁶-sulfanone



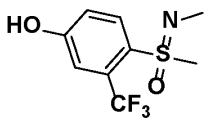
[0890] To a 0 °C solution of 4-methoxy-1-(methylsulfanyl)-2-(trifluoromethyl)benzene (10.5 g, 47.3 mmol) and $NH_2CO_2NH_4$ (14.8 g, 189 mmol) in MeOH (150 mL) was added $PhI(OAc)_2$ (38.1 g, 118 mmol). The mixture was stirred at room temperature for 16 h. The reaction mixture was quenched by addition of H_2O (300 mL) and then concentrated under reduced pressure to remove MeOH. The mixture was extracted with EtOAc (3 x 150 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 120 g cartridge, 0–70% EtOAc/Petroleum ether) to give imino[4-methoxy-2-(trifluoromethyl)phenyl]methyl-λ^6-sulfanone. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (d, J = 8.8 Hz, 1H), 7.47 – 7.36 (m, 2H), 4.43 (s, 1H), 3.91 (s, 3H), 3.07 (s, 3H).

Step 3: {[4-methoxy-2-(trifluoromethyl)phenyl](methyl)oxo-λ^6-sulfanylidene}(methyl)amine



[0891] To a solution of imino[4-methoxy-2-(trifluoromethyl)phenyl]methyl-λ^6-sulfanone (4.00 g, 15.8 mmol) in HCOOH (40 mL) was added 37% HCHO in H_2O (6.41 g, 79.0 mmol). The mixture was stirred at 100 °C for 16 h. After cooling to 0 °C, the reaction mixture was quenched by addition of H_2O (100 mL), and then adjusted to pH = 7 by dropwise addition of saturated aqueous Na_2CO_3 solution. The aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give {[4-methoxy-2-(trifluoromethyl)phenyl](methyl)oxo-λ^6-sulfanylidene}(methyl)amine, which was taken to the next step without further purification. MS = 268.1 $[M+H]^+$.

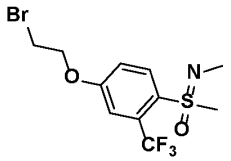
Step 4: 4-[methyl(methylimino)oxo-λ^6-sulfanyl]-3-(trifluoromethyl)phenol



[0892] To a 0 °C solution of {[4-methoxy-2-(trifluoromethyl)phenyl](methyl)oxo-λ^6-sulfanylidene}(methyl)amine (2.50 g, 9.35 mmol) in DCM (30 mL) was added BBr_3 (7.21 mL, 74.8

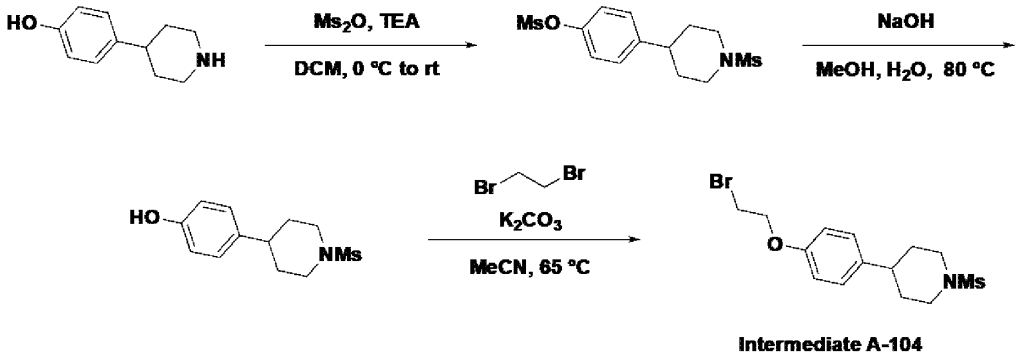
mmol). The mixture was stirred at room temperature for 3 h, then was quenched by slow addition of MeOH (200 mL). The mixture was stirred at room temperature for 10 min, then concentrated in vacuo. The residue was diluted with H_2O (100 mL) and extracted with EtOAc (6 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 4-[methyl(methylimino)oxo-λ^6-sulfanyl]-3-(trifluoromethyl)phenol, which was taken to the next step without further purification. MS = 254.1 $[M+H]^+$.

Step 5: {[4-(2-bromoethoxy)-2-(trifluoromethyl)phenyl](methyl)oxo-λ^6-sulfanylidene}(methyl)amine



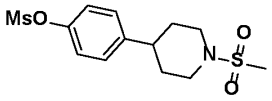
[0893] A mixture of 4-[methyl(methylimino)oxo-λ^6-sulfanyl]-3-(trifluoromethyl)phenol (2.00 g, 7.90 mmol), 1,2-dibromoethane (59.4 g, 316 mmol) and K_2CO_3 (8.73 g, 63.2 mmol) in MeCN (20 mL) was stirred at 65 °C for 16 h. After cooling to room temperature, the reaction mixture was quenched by addition of H_2O (30 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 20 g cartridge, 0–90% EtOAc/Petroleum ether) to give {[4-(2-bromoethoxy)-2-(trifluoromethyl)phenyl](methyl)oxo-λ^6-sulfanylidene}(methyl)amine (**Intermediate A-103**). MS = 360.0 / 362.0 $[M+H]^+$.

General Procedure for Intermediate A-104



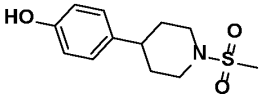
Intermediate A-104

Step 1: 4-(1-methanesulfonylpiperidin-4-yl)phenyl methanesulfonate



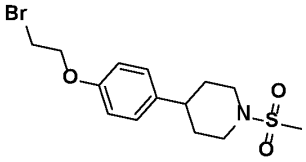
[0894] To a 0 °C solution of 4-(4-piperidyl)phenol hydrochloride (1.00 g, 4.68 mmol) and TEA (1.42 g, 14.0 mmol) in DCM (10 mL) was added Ms_2O (1.63 g, 9.36 mmol) in portions. The mixture was stirred at room temperature for 1 h. The reaction mixture was quenched by addition of H_2O (15 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 4-(1-methanesulfonylpiperidin-4-yl)phenyl methanesulfonate, which was taken to the next step without further purification.

Step 2: 4-(1-methanesulfonylpiperidin-4-yl)phenol



[0895] To a solution of [4-(1-methylsulfonyl-4-piperidyl)phenyl] methanesulfonate (1.30 g, 3.90 mmol) in MeOH (15 mL) and H_2O (10 mL) was added NaOH (1.19 g, 29.6 mmol). The mixture was stirred at 80 °C for 1 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure to remove MeOH and then adjusted to pH =1 by dropwise addition of 3.0 M aqueous HCl. The resulting precipitated solid was collected by filtration and dried in vacuo to give 4-(1-methanesulfonylpiperidin-4-yl)phenol, which was taken to the next step without further purification. MS = 256.2 $[M+H]^+$.

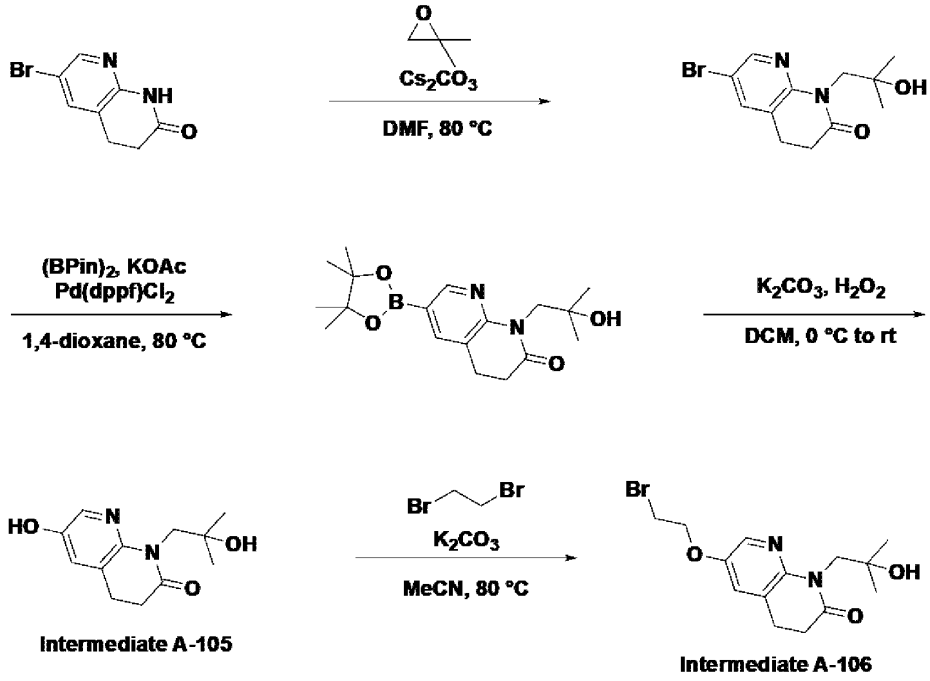
Step 3: 4-[4-(2-bromoethoxy)phenyl]-1-methanesulfonylpiperidine



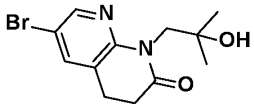
[0896] A mixture of 4-(1-methanesulfonylpiperidin-4-yl)phenol (600 mg, 2.35 mmol), 1,2-dibromoethane (17.7 g, 94.0 mmol) and K_2CO_3 (1.95 g, 14.1 mmol) in MeCN (10 mL) was stirred at 65 °C for 16 h. The reaction mixture was cooled to room temperature and quenched by addition of H_2O (15 mL), then extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica

gel chromatography (Biotage 12 g cartridge, 0–65% EtOAc/Petroleum ether) to give 4-[4-(2-bromoethoxy)phenyl]-1-methanesulfonylpiperidine (**Intermediate A-104**). MS = 364.1 / 362.1 $[M+H]^+$.

General Procedure for Intermediates A-105 & A-106



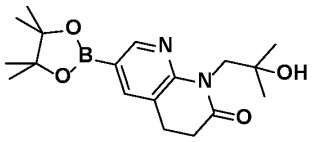
Step 1: 6-bromo-1-(2-hydroxy-2-methylpropyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-oneridin-2 –one



[0897] A mixture of 6-bromo-3,4-dihydro-1H-1,8-naphthyridin-2-one (2.00 g, 8.81 mmol), 2,2-dimethyloxirane (1.27 g, 17.6 mmol), and Cs_2CO_3 (4.30 g, 13.2 mmol) in DMF (30 mL) was stirred at 80 °C for 16 h. After cooling to 0 °C, the reaction mixture was quenched by addition of H_2O (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with saturated brine (2 x 50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–30%

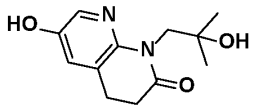
EtOAc/Petroleum ether) to give 6-bromo-1-(2-hydroxy-2-methylpropyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one. MS= 298.9 / 300.9 $[M+H]^+$.

Step 2: 1-(2-hydroxy-2-methylpropyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



[0898] A mixture of 6-bromo-1-(2-hydroxy-2-methylpropyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (900 mg, 3.01 mmol), bis(pinacolato)diboron (917 mg, 3.61 mmol), KOAc (591 mg, 6.02 mmol) and $Pd(dppf)Cl_2•CH_2Cl_2$ (246 mg, 301 μmol) in 1,4-dioxane (10 mL) was degassed and purged with N_2 (3x), and then the mixture was stirred at 80 °C for 16 h under N_2 atmosphere. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–50% EtOAc/Petroleum ether) to give 1-(2-hydroxy-2-methylpropyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one. MS= 347.3 $[M+H]^+$.

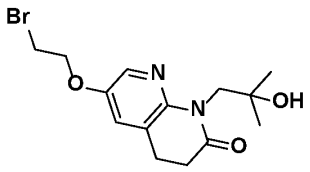
Step 3: 6-hydroxy-1-(2-hydroxy-2-methylpropyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one one



[0899] To a 0 °C solution of 1-(2-hydroxy-2-methylpropyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (800 mg, 2.31 mmol) and K_2CO_3 (639 mg, 4.62 mmol) in DCM (10 mL) was added 30% H_2O_2 in H_2O (0.577 mL, 6.00 mmol). The mixture was stirred at room temperature for 16 h. After cooling to 0 °C, the reaction mixture was quenched by addition of saturated aqueous Na_2SO_3 solution (20 mL). The mixture was diluted with H_2O (20 mL) and adjusted to pH = 6 by dropwise addition of 4.0 M aqueous HCl solution. The mixture was extracted with DCM (3 x 10 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–100% EtOAc/Petroleum ether) to give a crude product. The crude product was further triturated with petroleum ether (10 mL) at room temperature

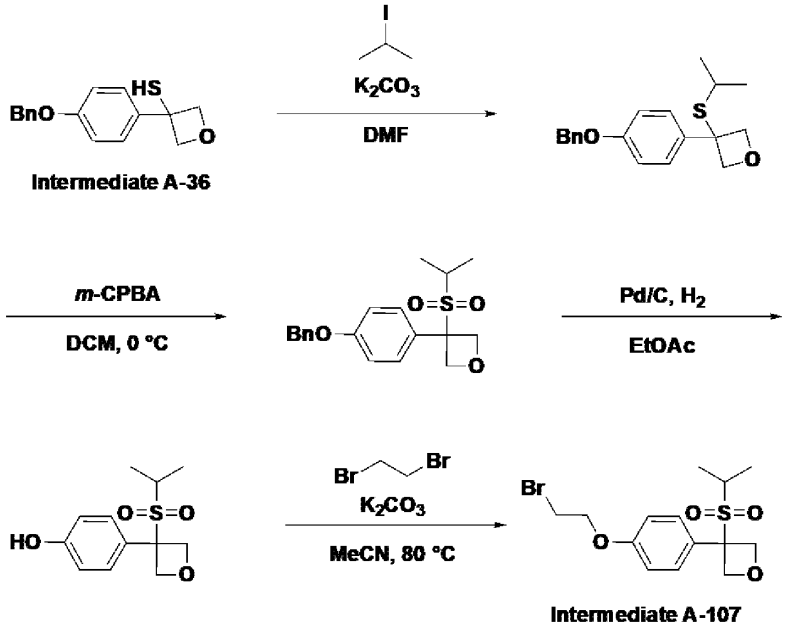
for 10 min and then filtered to give 6-hydroxy-1-(2-hydroxy-2-methylpropyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (**Intermediate A-105**). MS= 237.2 $[M+H]^+$.

Step 4: 6-(2-bromoethoxy)-1-(2-hydroxy-2-methylpropyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one

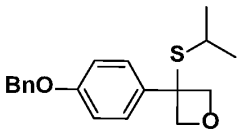


[0900] To a solution of 6-hydroxy-1-(2-hydroxy-2-methylpropyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (190 mg, 804 μmol) in MeCN (0.5 mL) was added K_2CO_3 (111 mg, 804 μmol) and 1,2-dibromoethane (6.04 g, 32.2 mmol). The mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 4 g cartridge, 0–100% EtOAc/Petroleum ether) to give 6-(2-bromoethoxy)-1-(2-hydroxy-2-methylpropyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (**Intermediate A-106**). MS = 343.1 / 345.1 $[M+H]^+$.

General Procedure for Intermediate A-107

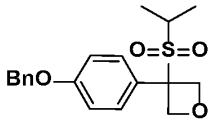


Step 1: 3-[4-(benzyloxy)phenyl]-3-(propan-2-ylsulfanyl)oxetane



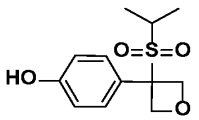
[0901] To a solution of 3-[4-(benzyloxy)phenyl]oxetane-3-thiol (**Step 3, Intermediate A-36,** 1.00 g, 3.67 mmol) in DMF (10 mL) was added K_2CO_3 (761 mg, 5.51 mmol) and 2-iodopropane (1.87 g, 11.0 mmol). The mixture was stirred at room temperature for 2 h. After cooling to 0 °C, the reaction mixture was quenched by addition of water (10 mL) and then extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–20% EtOAc/Petroleum ether) to give 3-[4-(benzyloxy)phenyl]-3-(propan-2-ylsulfanyl)oxetane. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.44 – 7.31 (m, 5H), 7.24 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H), 5.09 (s, 2H), 5.05 (d, J = 6.4 Hz, 2H), 4.74 (d, J = 6.4 Hz, 2H), 2.44 – 2.39 (m, 1H), 1.02 (d, J = 6.8 Hz, 6H).

Step 2: 3-[4-(benzyloxy)phenyl]-3-(propane-2-sulfonyl)oxetane



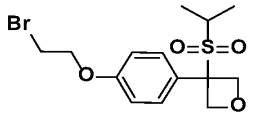
[0902] To a 0 °C solution of 3-(4-benzyloxyphenyl)-3-isopropylsulfanyl-oxetane (1.00 g, 3.18 mmol) in DCM (20 mL) was added *m*-CPBA (1.94 g, 85% purity, 9.54 mmol). The mixture was stirred at room temperature for 2 h. After cooling to 0 °C, the reaction mixture was quenched by addition of saturated aqueous Na_2SO_3 solution (20 mL), and then diluted with H_2O (10 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 3-(3-[4-(benzyloxy)phenyl]-3-(propane-2-sulfonyl)oxetane, which was taken to the next step without further purification. MS= 364.1 $[M + NH_4]^+$.

Step 3: 4-[3-(propane-2-sulfonyl)oxetan-3-yl]phenol



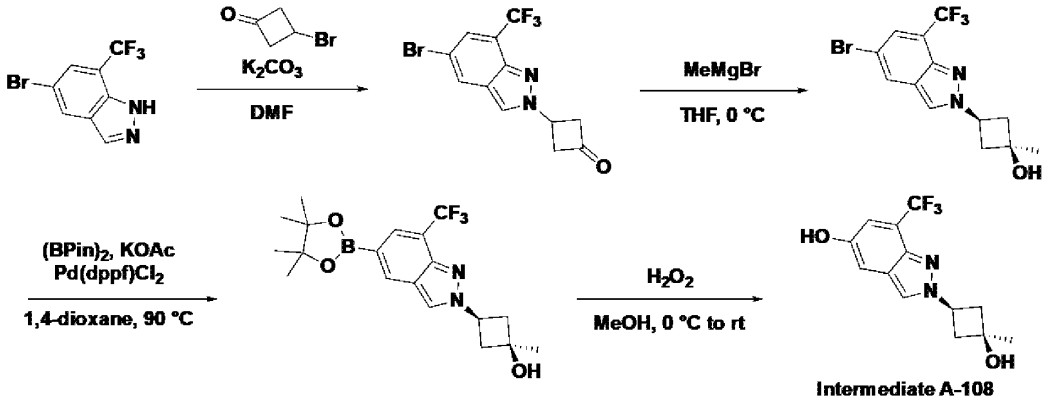
[0903] To a solution of 3-[4-(benzyloxy)phenyl]-3-(propane-2-sulfonyl)oxetane (1.00 g, 2.89 mmol) in EtOAc (20 mL) under Ar atmosphere was added Pd/C (2.00 g, 10 wt%, 1.89 mmol). The suspension was degassed in vacuo and purged with H_2. The mixture was stirred under H_2 (15 psi) at room temperature for 2 h. The mixture was filtered, and the filtrate was concentrated in vacuo to give 4-[3-(propane-2-sulfonyl)oxetan-3-yl]phenol, which was taken to the next step without further purification. MS= 274.1 $[M + NH_4]^+$.

Step 4: 3-[4-(2-bromoethoxy)phenyl]-3-(propane-2-sulfonyl)oxetane



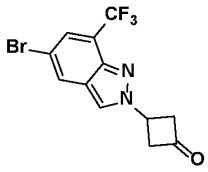
[0904] To a solution of 4-[3-(propane-2-sulfonyl)oxetan-3-yl]phenol (650 mg, 2.54 mmol) in MeCN (5 mL) was added K_2CO_3 (1.75 g, 12.7 mmol) and 1,2-dibromoethane (19.1 g, 101 mmol). The mixture was stirred at 65 °C for 15 h. After cooling to room temperature, the mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–50% EtOAc/Petroleum ether) to give 3-[4-(2-bromoethoxy)phenyl]-3-(propane-2-sulfonyl)oxetane (**Intermediate A-107**). MS= 380.0 / 382.0 $[M + NH_4]^+$.

General Procedure for Intermediate A-108



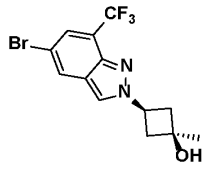
Intermediate A-108

Step 1: 3-[5-bromo-7-(trifluoromethyl)-2H-indazol-2-yl]cyclobutan-1-one



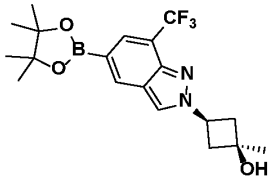
[0905] To a mixture of 5-bromo-7-(trifluoromethyl)-1H-indazole (950 mg, 3.58 mmol) and K_2CO_3 (991 mg, 7.17 mmol) in DMF (9 mL) at room temperature was added 3-bromocyclobutan-1-one (641 mg, 4.30 mmol) dropwise. The mixture was stirred at room temperature for 1 h. The mixture was then poured into ice water (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel chromatography (Biotage 50 g cartridge, 0–10% EtOAc/DCM) to give 3-[5-bromo-7-(trifluoromethyl)-2H-indazol-2-yl]cyclobutan-1-one (2nd eluting isomer). MS = 333.0 / 335.0 $[M+H]^+$.

Step 2: (*cis*)-3-[5-bromo-7-(trifluoromethyl)-2H-indazol-2-yl]-1-methylcyclobutan-1-ol



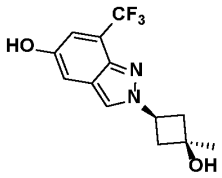
[0906] To a solution of 3-[5-bromo-7-(trifluoromethyl)-2H-indazol-2-yl]cyclobutan-1-one (995 mg, 2.99 mmol) in THF (10 mL) at 0 °C was added 3.0 M MeMgBr in Et_2O (1.29 mL, 3.88 mmol) dropwise. The resulting mixture was stirred at 0 °C for 1 h. The mixture was quenched by addition of saturated NH_4Cl solution (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography twice (Biotage 50 g cartridge, 0–50% EtOAc/DCM) to give (*cis*)-3-[5-bromo-7-(trifluoromethyl)-2H-indazol-2-yl]-1-methylcyclobutan-1-ol. MS = 349.1 / 351.1 $[M+H]^+$.

Step 3: (*cis*)-1-methyl-3-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-(trifluoromethyl)-2H-indazol-2-yl]cyclobutan-1-ol



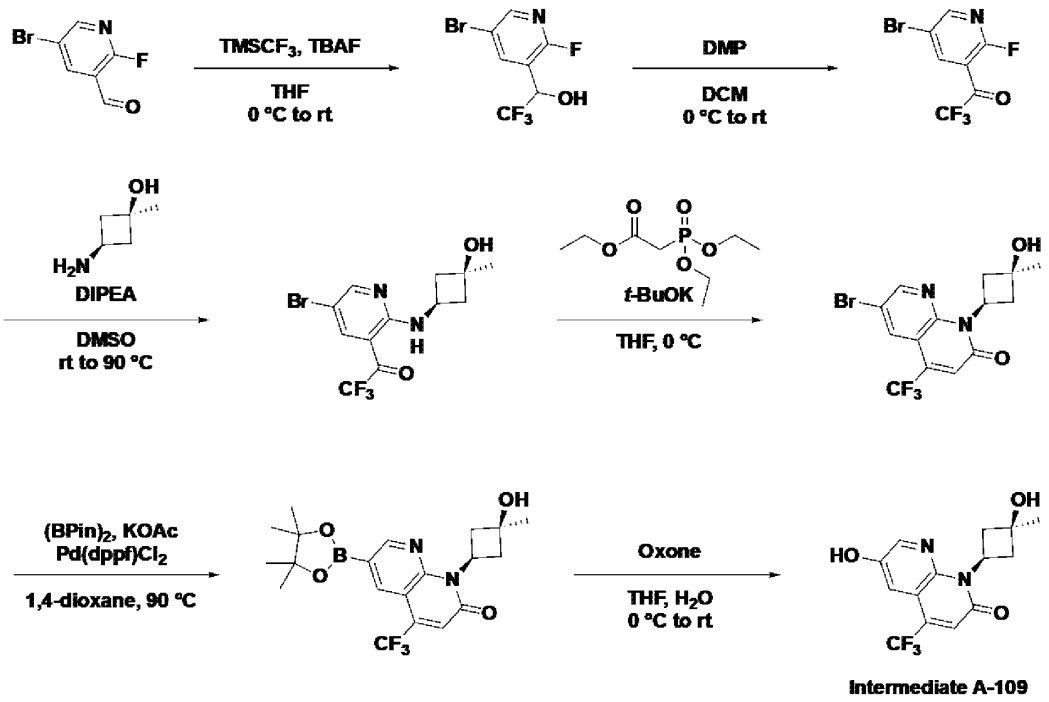
[0907] A mixture of (*cis*)-3-[5-bromo-7-(trifluoromethyl)-2H-indazol-2-yl]-1-methylcyclobutan-1-ol (800 mg, 2.29 mmol), bis(pinacolato)diboron (756 mg, 2.98 mmol), Pd(dppf)Cl_2 dichloromethane complex (93.6 mg, 0.115 mmol) and KOAc (450 mg, 4.58 mmol) in 1,4-dioxane (23 mL) was sparged with N_2 gas and then stirred at 90 °C for 16 h. The reaction mixture was cooled to room temperature and diluted with EtOAc, then filtered over a celite plug. The resulting filtrate was concentrated and used in the subsequent step without further purification. MS = 397.3 $[M+H]^+$.

Step 4: 2-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2H-indazol-5-ol

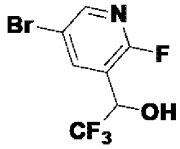


[0908] The crude residue from the previous step was dissolved in MeOH (11 mL) and cooled to 0 °C. A solution of 30% H_2O_2 in H_2O (0.585 mL, 5.72 mmol) was added dropwise. The mixture was then stirred at room temperature for 3 h. The mixture was concentrated under reduced pressure and purified by silica gel chromatography (Biotage 50 g cartridge, 0–50% EtOAc/DCM) to give 2-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2H-indazol-5-ol (**Intermediate A-108**). MS = 287.1 $[M+H]^+$.

General Procedure for Intermediate A-109

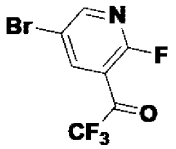


Step 1: 1-(5-bromo-2-fluoropyridin-3-yl)-2,2,2-trifluoroethan-1-ol



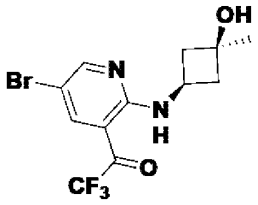
[0909] To a 0 °C mixture of 5-bromo-2-fluoro-pyridine-3-carbaldehyde (10.0 g, 49.0 mmol) and $TMSCF_3$ (8.36 g, 58.8 mmol) in THF (100 mL) was added dropwise 1.0 M TBAF in THF (9.80 mL, 9.80 mmol). The mixture was stirred at room temperature for 1 h, then was diluted with brine (150 mL) and extracted with EtOAc (2 x 80 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 120 g cartridge, 0–8% EtOAc/Petroleum ether) to provide 1-(5-bromo-2-fluoropyridin-3-yl)-2,2,2-trifluoroethan-1-ol. MS = 273.8 / 275.8 $[M+H]^+$.

Step 2: 1-(5-bromo-2-fluoropyridin-3-yl)-2,2,2-trifluoroethan-1-one



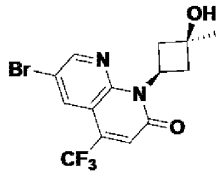
[0910] To a 0 °C mixture of 1-(5-bromo-2-fluoropyridin-3-yl)-2,2,2-trifluoroethan-1-ol (12.5 g, 45.6 mmol) in DCM (150 mL) was added Dess–Martin periodinane (23.2 g, 54.7 mmol). The mixture was stirred at room temperature for 16 h, then was quenched by addition of saturated aqueous Na_2SO_3 solution (200 mL) and extracted with DCM (2 x 80 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 120 g cartridge, 0–25% EtOAc/Petroleum ether) to provide 1-(5-bromo-2-fluoropyridin-3-yl)-2,2,2-trifluoroethan-1-one. MS = 289.8 / 291.8 $[M+H_2O+H]^+$.

Step 3: 1-(5-bromo-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}pyridin-3-yl)-2,2,2-trifluoroethan-1-one



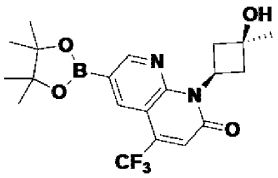
[0911] To a mixture of 1-(5-bromo-2-fluoropyridin-3-yl)-2,2,2-trifluoroethan-1-one (4.00 g, 14.7 mmol) and (*cis*)-3-amino-1-methylcyclobutan-1-ol (2.02 g, 14.7 mmol, HCl salt) in DMSO (35 mL) was added DIPEA (7.68 mL, 44.1 mmol). The mixture was stirred at 90 °C for 4 h. After cooling to room temperature, the mixture was diluted with H_2O (150 mL) and extracted with EtOAc (2 x 80 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 80 g cartridge, 0–25% EtOAc/Petroleum ether) to provide 1-(5-bromo-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}pyridin-3-yl)-2,2,2-trifluoroethan-1-one. MS = 352.9 / 354.8 $[M+H]^+$.

Step 4: 6-bromo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-4-(trifluoromethyl)-1,2-dihydro-1,8-naphthyridin-2-one



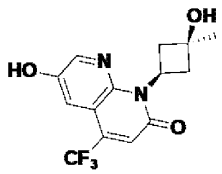
[0912] To a 0 °C mixture of ethyl 2-diethoxyphosphorylacetate (2.22 mL, 11.2 mmol) in THF (40 mL) was added *t*-BuOK (2.10 g, 18.7 mmol). The mixture was stirred at room temperature for 1 h, then cooled to 0 °C. A solution of 1-(5-bromo-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}pyridin-3-yl)-2,2,2-trifluoroethan-1-one (3.30 g, 9.34 mmol) in THF (25 mL) was added dropwise to the 0 °C mixture. After stirring at 0 °C for 2 h, the mixture was quenched by addition of saturated aqueous NH_4Cl solution (60 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 40 mL). The combined organic layers were concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 40 g cartridge, 0–17% EtOAc/Petroleum ether) to provide 6-bromo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-4-(trifluoromethyl)-1,2-dihydro-1,8-naphthyridin-2-one. MS = 377.0 / 378.9 $[M+H]^+$.

Step 5: 1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)-1,2-dihydro-1,8-naphthyridin-2-one



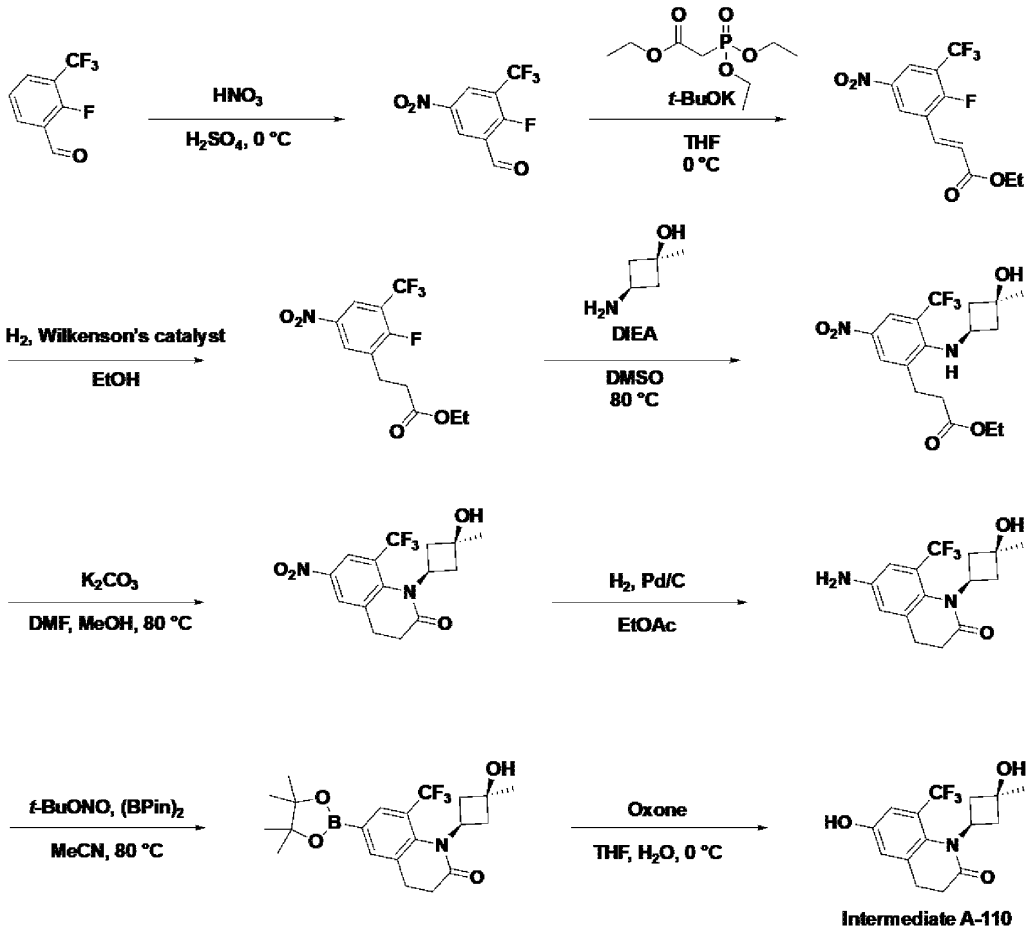
[0913] A mixture of 6-bromo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-4-(trifluoromethyl)-1,2-dihydro-1,8-naphthyridin-2-one (1.30 g, 3.45 mmol), bis(pinacolato)diboron (1.75 g, 6.89 mmol), KOAc (846 mg, 8.62 mmol) and $Pd(dppf)Cl_2$ (126 mg, 172 μmol) in 1,4-dioxane (20 mL) was purged with N_2 (3x) and stirred at 90 °C for 16 h. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo to provide 1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)-1,2-dihydro-1,8-naphthyridin-2-one, which was used in the subsequent step without further purification.

Step 6: 6-hydroxy-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-4-(trifluoromethyl)-1,2-dihydro-1,8-naphthyridin-2-one

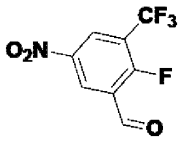


[0914] To a 0 °C mixture of 1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)-1,2-dihydro-1,8-naphthyridin-2-one (1.50 g, 3.54 mmol) in a THF (20 mL) and H_2O (10 mL) was added Oxone (2.61 g, 4.24 mmol). The mixture was stirred at room temperature for 1 h. The reaction mixture was cooled to 0–10 °C, quenched by addition of saturated Na_2SO_3 solution (60 mL) at 0–10 °C, and stirred for 30 min. The mixture was extracted with EtOAc (2 x 40 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 20 g cartridge, 0–15% EtOAc/Petroleum ether) to provide 6-hydroxy-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-4-(trifluoromethyl)-1,2-dihydro-1,8-naphthyridin-2-one (**Intermediate A-109**). MS = 315.0 $[M+H]^+$.

General Procedure for Intermediate A-110



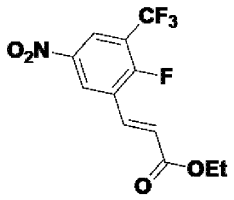
Step 1: 2-fluoro-5-nitro-3-(trifluoromethyl)benzaldehyde



[0915] To a 250 mL three-neck round bottom flask equipped with a magnetic stir bar and thermometer containing a solution of 2-fluoro-3-(trifluoromethyl)benzaldehyde (7.19 mL, 52.1 mmol) in H_2SO_4 (50 mL) at –5–0 °C was added HNO_3 (21.1 mL, 468 mmol) dropwise. The mixture was stirred at 0 °C for 30 min. The reaction mixture was poured into ice water (80 mL), adjusted to pH = 7 by addition of solid $NaHCO_3$, and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was

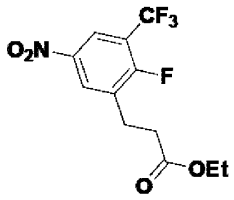
purified by flash silica gel chromatography (Biotage 40 g cartridge, 0–3% EtOAc/Petroleum ether) to provide 2-fluoro-5-nitro-3-(trifluoromethyl)benzaldehyde. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.43 (s, 1H), 8.96 (dd, J = 5.2, 2.8 Hz, 1H), 8.77 (dd, J = 5.6, 2.8 Hz, 1H).

Step 2: ethyl (2*E*)-3-[2-fluoro-5-nitro-3-(trifluoromethyl)phenyl]prop-2-enoate



[0916] To a 0 °C solution of ethyl 2-(diethoxyphosphoryl)acetate (13.8 mL, 69.6 mmol) in THF (300 mL) was added *t*-BuOK (8.52 g, 75.9 mmol) in portions. The mixture was stirred at 0 °C for 1 h. A solution of 2-fluoro-5-nitro-3-(trifluoromethyl)benzaldehyde (15.0 g, 63.3 mmol) in THF (30 mL) was added to the 0 °C mixture, and reaction was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched by addition of H_2O (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (80 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 80 g cartridge, 0–10% EtOAc/Petroleum ether) to provide ethyl (2*E*)-3-[2-fluoro-5-nitro-3-(trifluoromethyl)phenyl]prop-2-enoate. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.66 (dd, J = 5.6, 2.8 Hz, 1H), 8.53 (dd, J = 5.6, 2.8 Hz, 1H), 7.82 (d, J = 16.0 Hz, 1H), 6.72 (d, J = 16.0 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H).

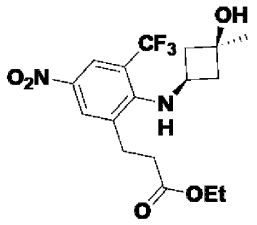
Step 3: ethyl 3-[2-fluoro-5-nitro-3-(trifluoromethyl)phenyl]propanoate



[0917] To a solution of ethyl (2*E*)-3-[2-fluoro-5-nitro-3-(trifluoromethyl)phenyl]prop-2-enoate (8.00 g, 26.0 mmol) in EtOH (200 mL) was added chlorotris(triphenylphosphine)rhodium(I) (1.20 g, 1.30 mmol). The suspension was degassed and purged with H_2 (3x). The mixture was stirred under H_2 (15 psi) at room temperature for 1 h. Solids were removed by filtration and the filtrate was concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 12 g

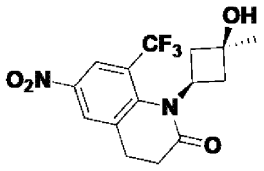
cartridge, 0–8% EtOAc/Petroleum ether) to provide ethyl 3-[2-fluoro-5-nitro-3-(trifluoromethyl)phenyl]propanoate. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.42 (s, 1H), 8.41 (s 1H), 4.19–4.13 (m, 2H), 3.13 (t, J = 7.2 Hz, 2H), 2.73 (t, J = 7.2 Hz, 2H), 1.26 (t, J = 7.2 Hz, 3H).

Step 4: ethyl 3-(5-nitro-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}-3-(trifluoromethyl)phenyl)propanoate



[0918] To a solution of ethyl 3-[2-fluoro-5-nitro-3-(trifluoromethyl)phenyl]propanoate (7.00 g, 22.6 mmol) in DMSO (100 mL) was added (*cis*)-3-amino-1-methylcyclobutan-1-ol (3.43 g, 24.9 mmol, HCl salt) and DIEA (11.8 mL, 67.9 mmol). The mixture was stirred at 80 °C for 12 h. After cooling to room temperature, the reaction mixture was quenched by addition of H_2O (80 mL) and extracted with EtOAc (3 x 80 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 40 g cartridge, 0–10% EtOAc/Petroleum ether) to provide ethyl 3-(5-nitro-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}-3-(trifluoromethyl)phenyl)propanoate. MS = 391.1 $[M+H]^+$.

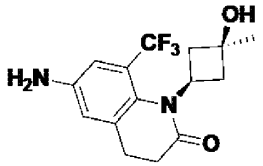
Step 5: 6-nitro-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-2-one



[0919] To a solution of ethyl 3-(5-nitro-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}-3-(trifluoromethyl)phenyl)propanoate (7.00 g, 17.9 mmol) in DMF (80 mL) and MeOH (10 mL) was added K_2CO_3 (7.44 g, 53.8 mmol). The mixture was stirred at 80 °C for 12 h. After cooling to room temperature, the reaction mixture was quenched by addition of H_2O (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (15 mL), dried over

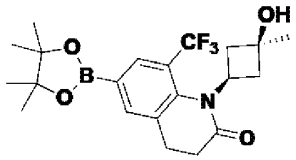
anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 40 g cartridge, 10–27% EtOAc/Petroleum ether) to provide 6-nitro-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-2-one. MS = 345.1 $[M+H]^+$.

Step 6: 6-amino-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-2-one



[0920] To a solution of 6-nitro-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-2-one (3.00 g, 8.71 mmol) in EtOAc (60 mL) under N_2 atmosphere was added Pd/C (244 mg, 10 wt%, 0.231 mmol). The suspension was degassed and purged with H_2 (3x). The mixture was stirred under H_2 (15 psi) at room temperature for 12 h. Solids were removed by filtration, and the filtrate was concentrated in vacuo to provide 6-amino-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-2-one, which was used in the subsequent step without further purification. MS = 315.1 $[M+H]^+$.

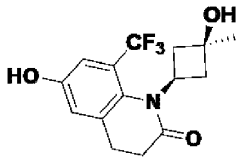
Step 7: 1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-2-one



[0921] To a solution of 6-amino-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-2-one (1.00 g, 3.18 mmol) in MeCN (10 mL) under N_2 atmosphere was added bis(pinacolato)diboron (970 mg, 3.82 mmol) and *tert*-butyl nitrite (492 mg, 4.77 mmol). The mixture was stirred at 80 °C for 2 h. After cooling to room temperature, the reaction mixture was quenched by addition of H_2O (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give 1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-

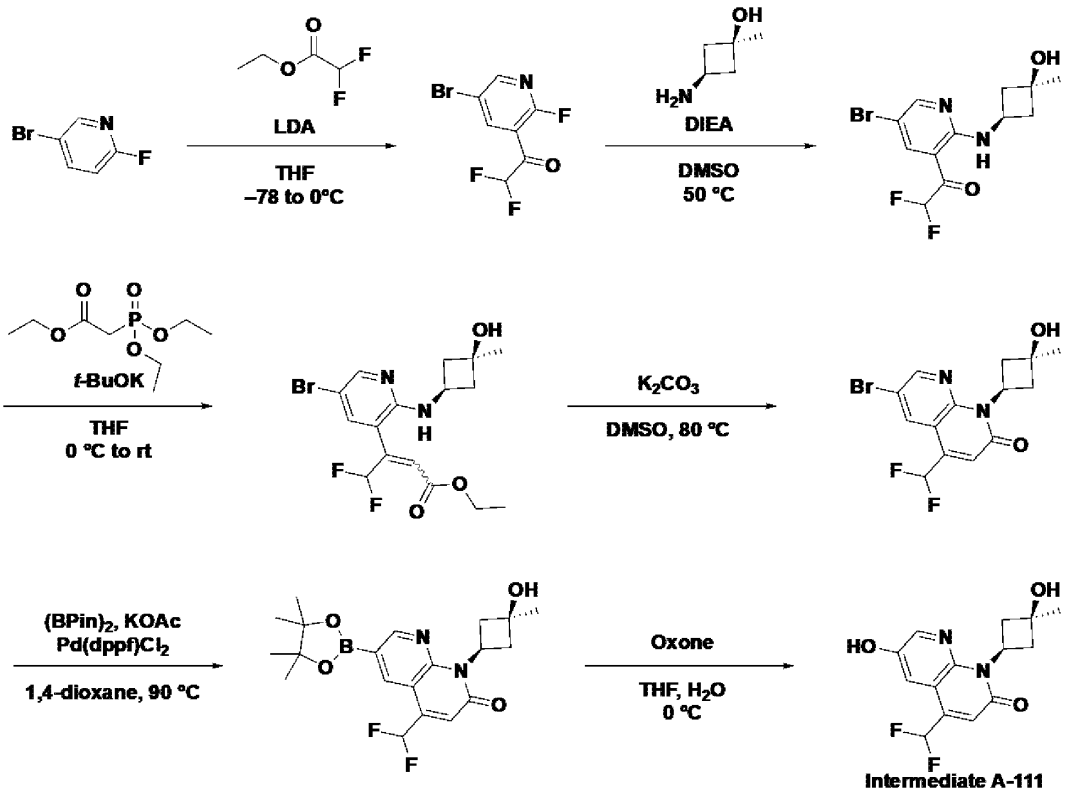
(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-2-one, which was used in the subsequent step without further purification. MS = 426.1 $[M+H]^+$.

Step 8: 6-hydroxy-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-2-one

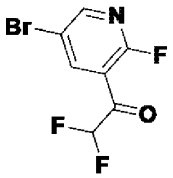


[0922] To a solution of 1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-2-one (800 mg, 1.88 mmol) in THF (9 mL) and H_2O (3 mL) was added Oxone (1.16 g, 1.88 mmol). The mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched by addition of saturated aqueous Na_2SO_3 (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give 6-hydroxy-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-2-one (**Intermediate A-110**), which was used in the subsequent step without further purification. MS = 316.0 $[M+H]^+$.

General Procedure for Intermediate A-111



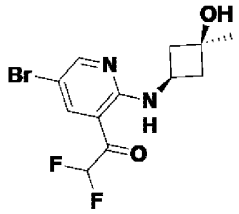
Step 1: 1-(5-bromo-2-fluoropyridin-3-yl)-2,2-difluoroethan-1-one



[0923] To a –78 °C mixture of 5-bromo-2-fluoro-pyridine (2.92 mL, 28.4 mmol) in THF (45 mL) under N_2 atmosphere was added 2.0 M LDA in THF (17.1 mL, 34.1 mmol). The mixture was stirred at –78 °C for 30 min under N_2 atmosphere, then a solution of ethyl 2,2-difluoroacetate (5.29 g, 42.6 mmol) in THF (5 mL) was added dropwise. The mixture was stirred at –78 °C for another 2 h under N_2 atmosphere, then was warmed to 0 °C. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl solution (50 mL) and then extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue

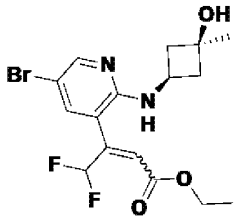
was purified by flash silica gel chromatography (Biotage 40 g cartridge, 0–20% EtOAc/Petroleum ether) to provide 1-(5-bromo-2-fluoropyridin-3-yl)-2,2-difluoroethan-1-one. MS = 272.0 / 273.9 $[M+H+H_2O]^+$.

Step 2: 1-(5-bromo-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}pyridin-3-yl)-2,2-difluoroethan-1-one



[0924] To a solution of 1-(5-bromo-2-fluoropyridin-3-yl)-2,2-difluoroethan-1-one (1.80 g, 7.09 mmol) and (*cis*)-3-amino-1-methylcyclobutan-1-ol (1.07 g, 7.80 mmol, HCl salt) in DMSO (20 mL) was added DIEA (4.94 mL, 28.4 mmol). The mixture was stirred at 50 °C for 2 h, then was cooled to 0 °C, quenched by addition of H_2O (20 mL), and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 20 g cartridge, 0–30% EtOAc/Petroleum ether) to provide 1-(5-bromo-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}pyridin-3-yl)-2,2-difluoroethan-1-one. MS = 335.0 / 336.9 $[M+H]^+$.

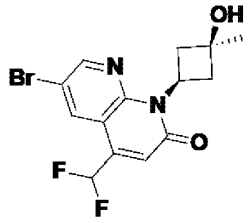
Step 3: ethyl 3-(5-bromo-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}pyridin-3-yl)-4,4-difluorobut-2-enoate



[0925] To a 0 °C mixture of ethyl 2-diethoxyphosphorylacetate (803 mg, 3.58 mmol) in THF (10 mL) was added *t*-BuOK (670 mg, 5.97 mmol). The mixture was allowed to warm to room temperature and stirred for 1 h, then cooled to 0 °C and a solution of 1-(5-bromo-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}pyridin-3-yl)-2,2-difluoroethan-1-one (1.00 g, 2.98 mmol) in THF (3 mL) was added dropwise. Then the mixture was stirred at 0 °C for 2 h, then was quenched

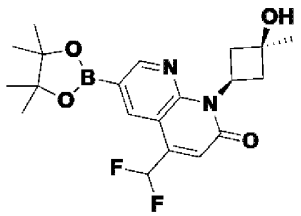
by addition of H_2O (15 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 20 g cartridge, 0–40% EtOAc/Petroleum ether) to provide ethyl 3-(5-bromo-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}pyridin-3-yl)-4,4-difluorobut-2-enoate. MS = 405.0 / 407.0 $[M+H]^+$.

Step 4: 6-bromo-4-(difluoromethyl)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1,2-dihydro-1,8-naphthyridin-2-one



[0926] To a mixture of ethyl 3-(5-bromo-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}pyridin-3-yl)-4,4-difluorobut-2-enoate (730 mg, 1.80 mmol) in DMSO (10 mL) was added K_2CO_3 (747 mg, 5.40 mmol). The mixture was stirred at 80 °C for 2. After cooling to room temperature, the reaction mixture was quenched by addition of H_2O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–35% EtOAc/Petroleum ether) to provide 6-bromo-4-(difluoromethyl)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1,2-dihydro-1,8-naphthyridin-2-one. MS = 359.0 / 361.0 $[M+H]^+$.

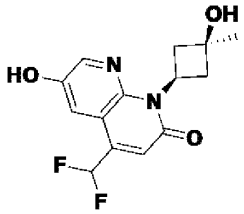
Step 5: 4-(difluoromethyl)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-1,8-naphthyridin-2-one



[0927] A mixture of 6-bromo-4-(difluoromethyl)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1,2-dihydro-1,8-naphthyridin-2-one (300 mg, 835 μmol), bis(pinacolato)diboron (318 mg, 1.25 mmol), KOAc (205 mg, 2.09 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (34.1 mg, 41.8 μmol) in 1,4-dioxane (4 mL)

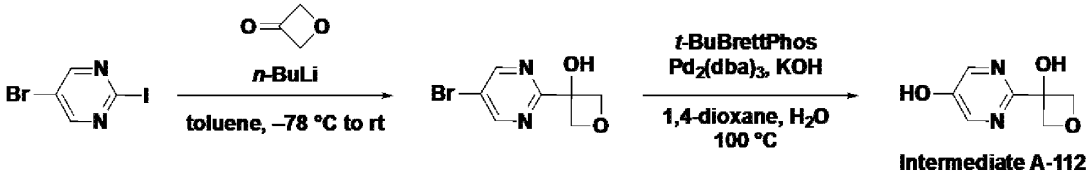
was degassed and purged with N_2 (3x), and then stirred at 90 °C for 12 h under N_2 atmosphere. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo to give 4-(difluoromethyl)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-1,8-naphthyridin-2-one, which was used in the subsequent step without further purification.

Step 6: 4-(difluoromethyl)-6-hydroxy-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1,2-dihydro-1,8-naphthyridin-2-one

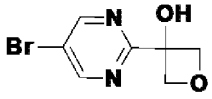


[0928] To a 0 °C solution of 4-(difluoromethyl)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-1,8-naphthyridin-2-one (400 mg, 985 μmol) in THF (5 mL) and H_2O (2 mL) was added Oxone (424 mg, 689 μmol). The mixture was stirred at 0 °C for 1 h, and then was quenched with saturated aqueous Na_2SO_3 solution (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 4 g cartridge, 0–40% EtOAc/Petroleum ether) to provide 4-(difluoromethyl)-6-hydroxy-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1,2-dihydro-1,8-naphthyridin-2-one (**Intermediate A-111**). MS = 297.0 $[M+H]^+$.

General Procedure for Intermediate A-112

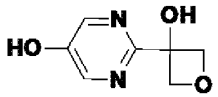


Step 1: 3-(5-bromopyrimidin-2-yl)oxetan-3-ol



[0929] To a –78 °C mixture of 5-bromo-2-iodo-pyrimidine (5.00 g, 17.6 mmol) in toluene (40 mL) under N_2 atmosphere was added 2.5 M *n*-BuLi in *n*-hexane (7.37 mL, 18.4 mmol) dropwise. The mixture was stirred at –78 °C for 30 min under N_2 atmosphere and then a solution of oxetan-3-one (1.52 g, 21.1 mmol) in toluene (20 mL) was added dropwise. The resulting mixture was stirred at –78 °C for 30 min and then stirred at room temperature for 1 h. The reaction mixture was cooled to 0 °C, quenched by addition of saturated aqueous NH_4Cl solution (50 mL), then extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 40 g cartridge, 100% EtOAc) to provide 3-(5-bromopyrimidin-2-yl)oxetan-3-ol. MS = 231.0 / 233.0 $[M+H]^+$.

Step 2: 2-(3-hydroxyoxetan-3-yl)pyrimidin-5-ol



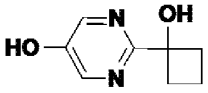
[0930] A mixture of 3-(5-bromopyrimidin-2-yl)oxetan-3-ol (1.00 g, 4.33 mmol), $Pd_2(dba)_3$ (79.3 mg, 86.6 µmol), KOH (729 mg, 13.0 mmol) and ditert-butyl-[2,3,4,5-tetramethyl-6-(2,4,6-triisopropylphenyl)phenyl]phosphane (208 mg, 433 µmol) in 1,4-dioxane (10 mL) and H_2O (5 mL) was degassed and purged with N_2 (3x) and then stirred at 100 °C for 4 h under N_2 atmosphere. The reaction mixture was cooled to room temperature, quenched by addition of H_2O (20 mL), and then extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 25 g cartridge, 0–100% EtOAc/Petroleum ether) to provide 2-(3-hydroxyoxetan-3-yl)pyrimidin-5-ol (**Intermediate A-112**). MS =169.1 $[M+H]^+$.

[0931] The following intermediates in Table 11.2 were prepared according to procedures analogous to those described for **Intermediate A-112** using the appropriate starting materials or common intermediates.

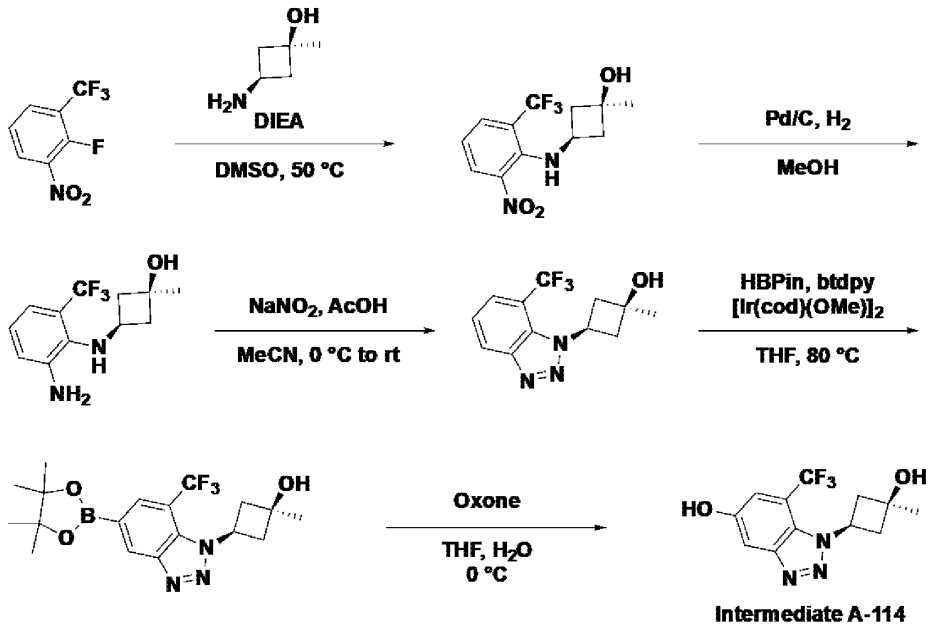
General Procedure for Intermediate A-113

Table 11.2

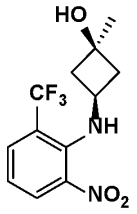
Intermediate	Structure	IUPAC Name	Exact Mass $[M+H]^+$

A-113		2-(1-hydroxycyclobutyl)pyrimidin-5-ol	Calc'd 167.1 Found 167.1

General Procedure for Intermediate A-114



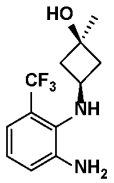
Step 1: (*cis*)-1-methyl-3-{[2-nitro-6-(trifluoromethyl)phenyl]amino}cyclobutan-1-ol



[0932] A mixture of 2-fluoro-1-nitro-3-(trifluoromethyl)benzene (1.50 g, 7.17 mmol), DIEA (3.71 g, 28.7 mmol) and (*cis*)-3-amino-1-methylcyclobutan-1-ol (1.09 g, 7.89 mmol, HCl salt) in DMSO (15 mL) was stirred at 50 °C for 2 h. After cooling to room temperature, the reaction mixture was poured into H_2O (50 mL). The mixture was extracted with EtOAc (3 x 60 mL). The combined organic layers were washed with brine (2 x 40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give (*cis*)-1-methyl-3-{[2-nitro-6-

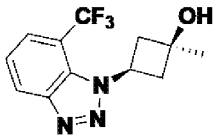
(trifluoromethyl)phenyl]amino}cyclobutan-1-ol, which was taken to the next step without further purification. MS = 290.9 $[M+H]^+$.

Step 2: (*cis*)-3-amino-1-methylcyclobutan-1-ol



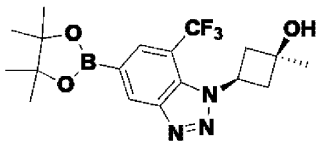
[0933] To a mixture of Pd/C (4.00 g, 10 wt%, 3.78 mmol) in MeOH (100 mL) was added (*cis*)-1-methyl-3-{[2-nitro-6-(trifluoromethyl)phenyl]amino}cyclobutan-1-ol (6.00 g, 20.67 mmol). The mixture was stirred at room temperature for 2 h under H_2 (15 psi) atmosphere. The mixture was filtered and the filtrate was concentrated in vacuo to give (*cis*)-3-amino-1-methylcyclobutan-1-ol, which was taken to the next step without further purification MS = 261.0 $[M+H]^+$.

Step 3: (*cis*)-1-methyl-3-[7-(trifluoromethyl)-1H-1,2,3-benzotriazol-1-yl]cyclobutan-1-ol



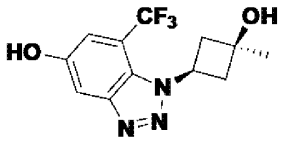
[0934] To a 0 °C mixture of 3-[2-amino-6-(trifluoromethyl)anilino]-1-methyl-cyclobutanol (2.00 g, 7.68 mmol) in AcOH (4 mL) and MeCN (20 mL) was added $NaNO_2$ (1.06 g, 15.4 mmol). The mixture was allowed to warm to room temperature and stirred for 16 h. The mixture was diluted with saturated $NaHCO_3$ solution (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give (*cis*)-1-methyl-3-[7-(trifluoromethyl)-1H-1,2,3-benzotriazol-1-yl]cyclobutan-1-ol, which was used in the subsequent step without further purification. MS = 272.0 $[M+H]^+$.

Step 4: (*cis*)-1-methyl-3-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-(trifluoromethyl)-1H-1,2,3-benzotriazol-1-yl]cyclobutan-1-ol



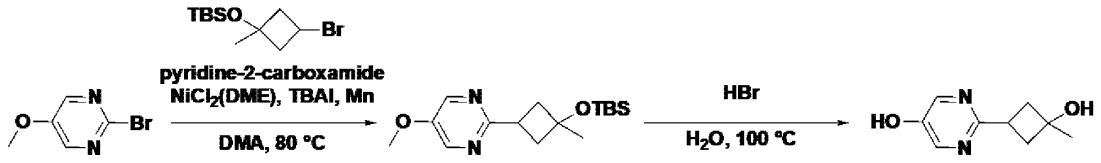
[0935] A mixture of (*cis*)-1-methyl-3-[7-(trifluoromethyl)-1H-1,2,3-benzotriazol-1-yl]cyclobutan-1-ol (2.30 g, 8.48 mmol), pinacolborane (12.3 mL, 84.8 mmol), 4,4-di-*tert*-butyl-2,2'-dipyridine (228 mg, 0.848 mmol) and (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (281 mg, 0.424 mmol) in THF (30 mL) was degassed with N_2 for 10 min, and then stirred at 80 °C for 16 h under N_2 atmosphere. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated in vacuo to give (*cis*)-1-methyl-3-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-(trifluoromethyl)-1H-1,2,3-benzotriazol-1-yl]cyclobutan-1-ol, which was used in the next step without further purification.

Step 5: 1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,2,3-benzotriazol-5-ol

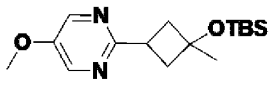


[0936] To a 0 °C solution of (*cis*)-1-methyl-3-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-(trifluoromethyl)-1H-1,2,3-benzotriazol-1-yl]cyclobutan-1-ol (3.3 g, 8.31 mmol) in THF (20 mL) and H_2O (10 mL) was added Oxone (15.3 g, 24.9 mmol). The mixture was stirred at 0 °C for 2 h. The mixture was quenched with saturated aqueous Na_2SO_3 solution. The mixture was extracted with chloroform (3 x 30 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 40 g cartridge, 0–60% EtOAc/Petroleum ether) to provide 1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,2,3-benzotriazol-5-ol (**Intermediate A-114**). MS = 288.0 $[M+H]^+$.

General Procedure for Intermediate A-115

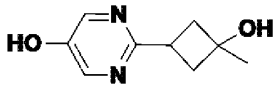


Step 1: 2-{3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl}-5-methoxypyrimidine



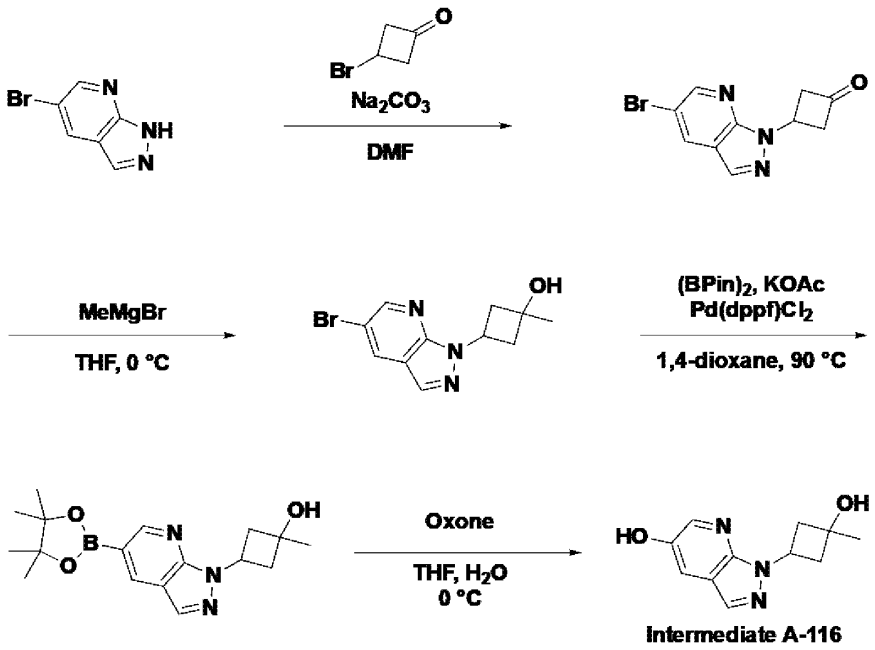
[0937] In a glove box, to a vial equipped with a magnetic stir bar was added 2-bromo-5-methoxypyrimidine (1.00 g, 5.30 mmol) and (3-bromo-1-methyl-cyclobutoxy)-*tert*-butyl-dimethyl-silane (7.40 g, 26.5 mmol) in DMA (80 mL). To the mixture was added manganese (3.49 g, 63.5 mmol), pyridine-2-carboxamidine hydrochloride (2.50 g, 15.9 mmol), TBAI (1.35 g, 3.65 mmol) and dichloro(dimethoxyethane)nickel (872 mg, 3.97 mmol). The reaction was purged with Ar for 10 min, and then stirred at 80 °C for 12 h. After cooling to room temperature, the reaction mixture was quenched with H_2O (50 mL) and filtered to remove solids. The filtrate was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 40 g cartridge, 0–25% EtOAc/Petroleum ether) to provide 2-{3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl}-5-methoxypyrimidine. MS = 309.4 $[M+H]^+$.

Step 2: 2-(3-hydroxy-3-methylcyclobutyl)pyrimidin-5-ol



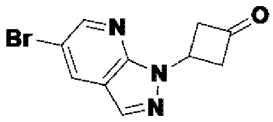
[0938] To a solution of 2-{3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl}-5-methoxypyrimidine (350 mg, 1.13 mmol) in H_2O (7 mL) was added HBr (7.00 mL, 51.6 mmol). The mixture was stirred at 100 °C for 30 h. After cooling to room temperature, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ solution (15 mL), then extracted with EtOAc (3 x 20 mL). The combined organic layers were concentrated in vacuo. The residue was purified by reverse phase preparative HPLC (Phenomenex Luna C_{18} column, 1–20% MeCN:10 mM TFA in H_2O) to provide 2-(3-hydroxy-3-methylcyclobutyl)pyrimidin-5-ol (**Intermediate A-115**). MS = 181.0 $[M+H]^+$.

General Procedure for Intermediate A-116



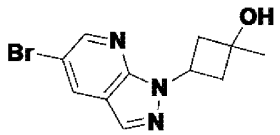
Intermediate A-116

Step 1: 3-{5-bromo-1H-pyrazolo[3,4-b]pyridin-1-yl}cyclobutan-1-one



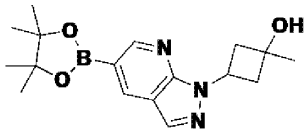
[0939] To a solution of 5-bromo-1H-pyrazolo[3,4-b]pyridine (5.00 g, 25.3 mmol) in DMF (45 mL) was added Na_2CO_3 (5.35 g, 50.5 mmol). The mixture was stirred at room temperature for 10 min, and then a solution 3-bromocyclobutanone (8.28 g, 55.6 mmol) in DMF (5 mL) was added dropwise by syringe pump over 2 h. The resulting mixture was stirred at room temperature for 3 h, then was quenched by addition of H_2O (50 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 80 g cartridge, 0–100% EtOAc/Petroleum ether) to provide 3-{5-bromo-1H-pyrazolo[3,4-b]pyridin-1-yl}cyclobutan-1-one (1st eluting isomer). MS = 266.0 / 268.0 $[M+H]^+$.

Step 2: 3-{5-bromo-1H-pyrazolo[3,4-b]pyridin-1-yl}-1-methylcyclobutan-1-ol



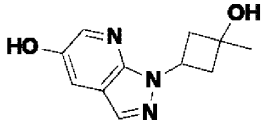
[0940] To a 0 °C solution of 3-(5-bromopyrazolo[3,4-b]pyridin-1-yl)cyclobutanone (400 mg, 1.50 mmol) in THF (4 mL) under N_2 atmosphere was added 3.0 M MeMgBr in THF (0.55 mL, 1.65 mmol) dropwise. The mixture was stirred at 0 °C for 3 h under N_2 atmosphere. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl solution (15 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 40 g cartridge, 0–25% EtOAc/Petroleum ether) to provide 3-{5-bromo-1H-pyrazolo[3,4-b]pyridin-1-yl}-1-methylcyclobutan-1-ol. MS = 282.0 / 284.0 $[M+H]^+$.

Step 3: 1-methyl-3-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazolo[3,4-b]pyridin-1-yl]cyclobutan-1-ol



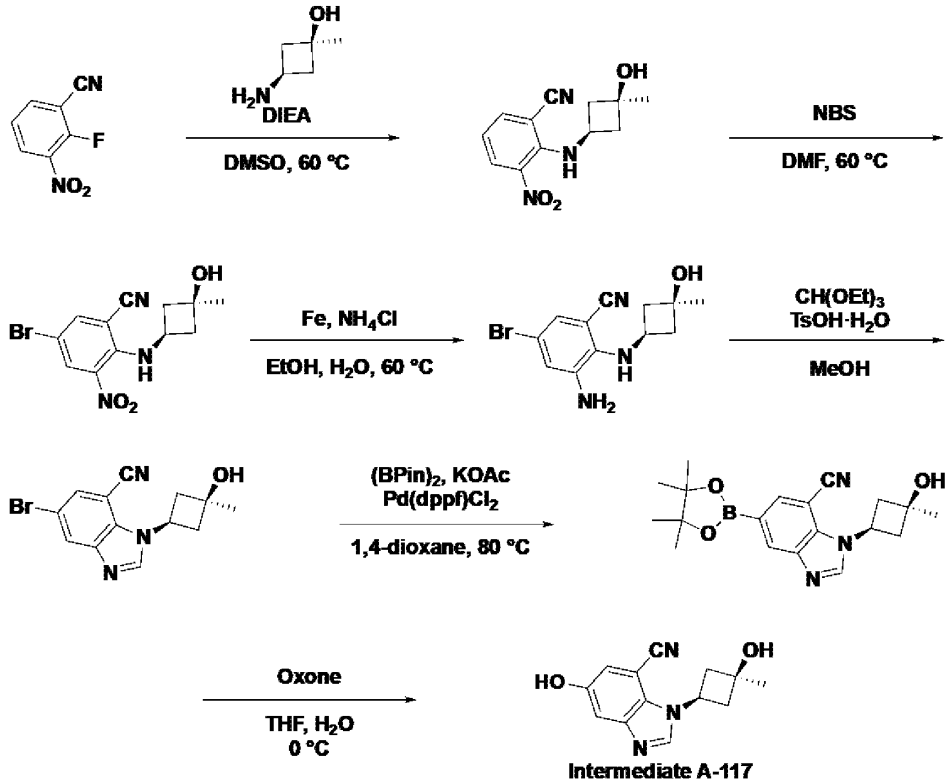
[0941] A mixture of 3-{5-bromo-1H-pyrazolo[3,4-b]pyridin-1-yl}-1-methylcyclobutan-1-ol (170 mg, 0.603 mmol), bis(pinacolato)diboron (184 mg, 0.723 mmol), KOAc (148 mg, 1.51 mmol), $Pd(dppf)Cl_2•CH_2Cl_2$ (49.1 mg, 60.3 μmol) in 1,4-dioxane (3.3 mL) was degassed and purged with N_2 (3x), and then the mixture was stirred at 90 °C for 12 h under N_2 atmosphere. The reaction mixture was allowed to cool to room temperature, then was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide 1-methyl-3-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazolo[3,4-b]pyridin-1-yl]cyclobutan-1-ol, which was used in the subsequent step without further purification. MS = 330.2 $[M+H]^+$.

Step 4. 1-(3-hydroxy-3-methylcyclobutyl)-1H-pyrazolo[3,4-b]pyridin-5-ol

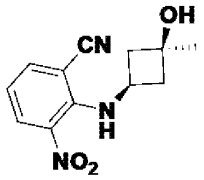


[0942] To a 0 °C solution of 1-methyl-3-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazolo[3,4-b]pyridin-1-yl]cyclobutan-1-ol (330 mg, 1.00 mmol) in THF (5 mL) and H_2O (2.5 mL) was added Oxone (616 mg, 1.00 mmol). The mixture was stirred at 0 °C for 1 h, then was quenched by addition of saturated aqueous Na_2SO_3 solution. The mixture was extracted with chloroform (3 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 4 g cartridge, 0–60% EtOAc/Petroleum ether) to provide 1-(3-hydroxy-3-methylcyclobutyl)-1H-pyrazolo[3,4-b]pyridin-5-ol (**Intermediate A-116**). MS = 220.1 $[M+H]^+$.

General Procedure for Intermediate A-117

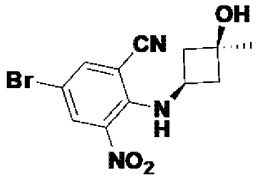


Step 1: 3-nitro-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}benzonitrile



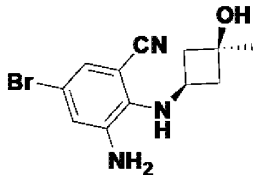
[0943] To a solution of 2-fluoro-3-nitro-benzonitrile (2.50 g, 15.1 mmol) in DMSO (25 mL) was added DIEA (7.86 mL, 45.2 mmol) and (*cis*)-3-amino-1-methylcyclobutan-1-ol (1.67 g, 16.6 mmol). The mixture was stirred at 60 °C for 1 h. After cooling to room temperature, the mixture was diluted with H_2O (30 mL), filtered, and concentrated in vacuo to give 3-nitro-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}benzonitrile, which was used in the subsequent step without further purification. MS = 248.3 $[M+H]^+$.

Step 2: 5-bromo-3-nitro-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}benzonitrile



[0944] To a solution of 3-nitro-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}benzonitrile (2.50 g, 10.1 mmol) in DMF (25 mL) was added NBS (3.60 g, 20.2 mmol). The mixture was stirred at 60 °C for 16 h. After cooling to room temperature, the mixture was diluted with H_2O (30 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 40 g cartridge, 0–15% EtOAc/Petroleum ether) to provide 5-bromo-3-nitro-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}benzonitrile.

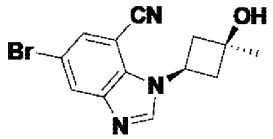
Step 3: 5-bromo-3-nitro-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}benzonitrile



[0945] To a solution of 5-bromo-3-nitro-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}benzonitrile (2.00 g, 6.13 mmol) in EtOH (20 mL) and H_2O (10 mL) was added Fe (3.42 g, 61.3 mmol) and NH_4Cl (4.92 g, 92.0 mmol). The mixture was stirred at 60 °C for

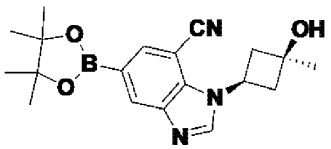
2 h. After cooling to room temperature, solids were removed by filtration. The filtrate was diluted with H_2O (30 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give 5-bromo-3-nitro-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}benzonitrile, which was used in the subsequent step without further purification. MS= 295.9 / 297.9 $[M+H]^+$.

Step 4: 5-bromo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazole-7-carbonitrile



[0946] To a solution of 5-bromo-3-nitro-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}benzonitrile (1.80 g, 6.08 mmol) in MeOH (15 mL) was added triethyl orthoformate (3.03 mL, 18.23 mmol) and $TsOH•H_2O$ (116 mg, 0.608 mmol). The mixture was stirred at room temperature for 16 h. The mixture was diluted with H_2O (30 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 40 g cartridge, 0–70% EtOAc/Petroleum ether) to provide 5-bromo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazole-7-carbonitrile. MS = 305.8 / 307.9 $[M+H]^+$.

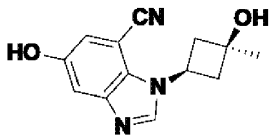
Step 5: 1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-1,3-benzodiazole-7-carbonitrile



[0947] To a solution of 5-bromo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazole-7-carbonitrile (1.15 g, 3.76 mmol) in 1,4-dioxane (20 mL) was added bis(pinacolato)diboron (4.77 g, 18.8 mmol), KOAc (737 mg, 7.51 mmol), and $Pd(dppf)Cl_2$ (275 mg, 376 µmol). The mixture was degassed and purged with N_2 for 10 min, and then stirred at 80 °C for 16 h under N_2 atmosphere. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo to give 1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5-(4,4,5,5-tetramethyl-1,3,2-

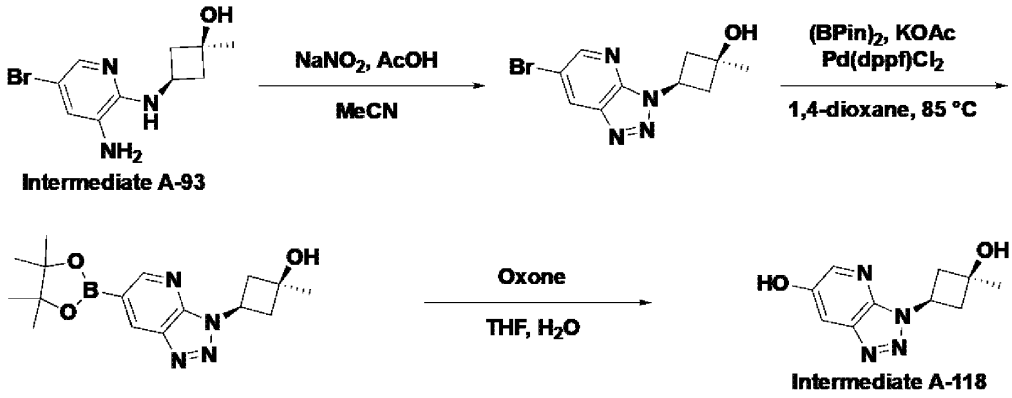
dioxaborolan-2-yl)-1H-1,3-benzodiazole-7-carbonitrile, which was used in the subsequent step without further purification.

Step 6: 5-hydroxy-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazole-7-carbonitrile



[0948] To a 0 °C solution of 1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-1,3-benzodiazole-7-carbonitrile (1.30 g, 3.68 mmol) in THF (10 mL) and H_2O (10 mL) was added Oxone (2.26 g, 3.68 mmol). The mixture was stirred at room temperature for 2 h, then was diluted with H_2O (30 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 20 g cartridge, 0–80% EtOAc/Petroleum ether) to provide 5-hydroxy-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazole-7-carbonitrile (**Intermediate A-117**). MS= 244.0 $[M+H]^+$.

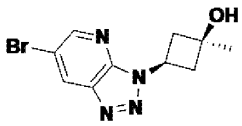
General Procedure for Intermediate A-118



Intermediate A-93

Intermediate A-118

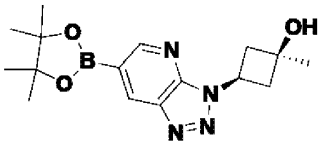
Step 1: (*cis*)-3-{6-bromo-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl}-1-methylcyclobutan-1-ol



[0949] To a solution of (*cis*)-3-[(3-amino-5-bromopyridin-2-yl)amino]-1-methylcyclobutan-1-ol (**Intermediate A-93**, 1.00 g, 3.67 mmol) in AcOH (10 mL) and MeCN (3 mL) was added $NaNO_2$

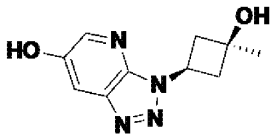
(507 mg, 7.35 mmol). The mixture was stirred at room temperature for 3 h. The mixture was diluted with H_2O (30 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give (*cis*)-3-{6-bromo-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl}-1-methylcyclobutan-1-ol, which was used in the subsequent step without further purification. MS= 282.8 / 284.9 $[M+H]^+$.

Step 2: (*cis*)-1-methyl-3-[6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl]cyclobutan-1-ol



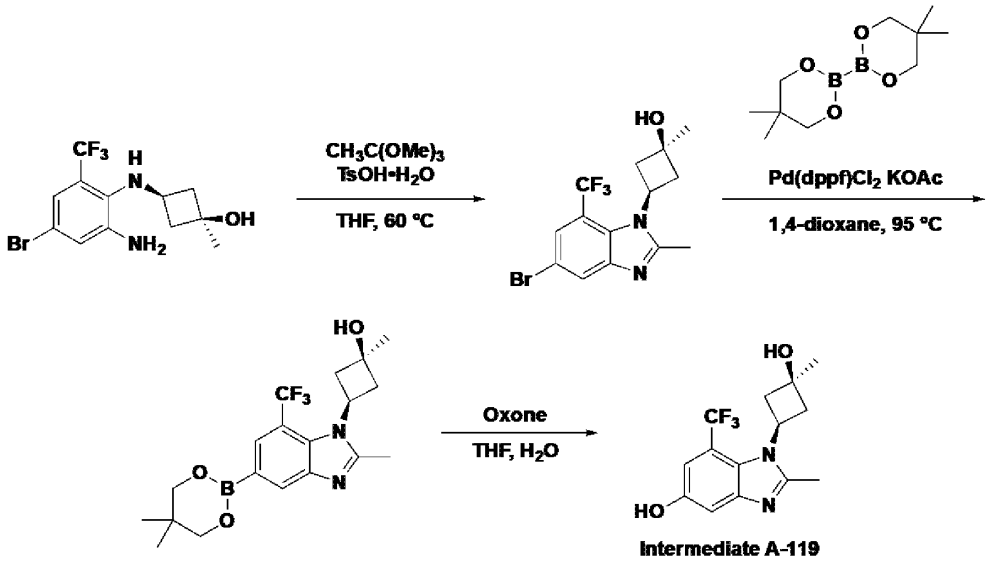
[0950] A mixture of (*cis*)-3-{6-bromo-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl}-1-methylcyclobutan-1-ol (400 mg, 1.41 mmol), bis(pinacolato)diboron (431 mg, 1.70 mmol), KOAc (277 mg, 2.83 mmol) and Pd(dppf)Cl_2 (103 mg, 141 μmol) in 1,4-dioxane (10 mL) was degassed and purged with N_2 for 10 min, and then stirred at 85 °C for 16 h. Solids were removed by filtration and the filtrate was concentrated in vacuo to give (*cis*)-1-methyl-3-[6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl]cyclobutan-1-ol, which was taken to the next step without further purification.

Step 3: 3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-3H-[1,2,3]triazolo[4,5-b]pyridin-6-ol

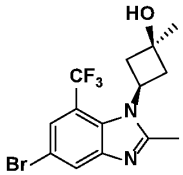


[0951] To a solution of (*cis*)-1-methyl-3-[6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl]cyclobutan-1-ol (400 mg, 1.21 mmol) in THF (5 mL) and H_2O (5 mL) was added Oxone (745 mg, 1.21 mmol). The mixture was stirred at room temperature for 1 h, and then was concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–85% EtOAc/Petroleum ether) to provide 3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-3H-[1,2,3]triazolo[4,5-b]pyridin-6-ol (**Intermediate A-118**). MS = 221.2 $[M+H]^+$.

General Procedure for Intermediate A-119

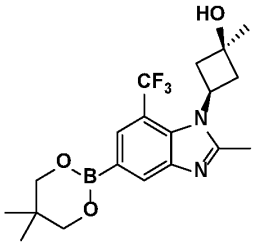


Step 1: (*cis*)-3-(5-bromo-2-methyl-7-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)-1-methylcyclobutan-1-ol



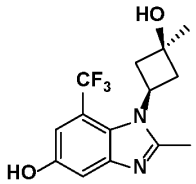
[0952] To a solution of (*cis*)-3-{[2-amino-4-bromo-6-(trifluoromethyl)phenyl]amino}-1-methylcyclobutan-1-ol (General procedure for **Intermediate A-92**, Step 3, 2.00 g, 5.90 mmol) and 1,1,1-trimethoxyethane (2.13 g, 17.7 mmol) in THF (30 mL) was added TsOH•H_2O (112 mg, 589 μmol). The mixture was stirred at 60 °C for 16 h. The mixture was diluted with H_2O (30 mL) and extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 40 g cartridge, 0–50% EtOAc/Petroleum ether) to give (*cis*)-3-(5-bromo-2-methyl-7-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)-1-methylcyclobutan-1-ol. MS = 363.0 / 365.0 $[M+H]^+$.

Step 2: (*cis*)-3-(5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-2-methyl-7-(trifluoromethyl)-1H-benzo[d]imidazole-1-yl)-1-methylcyclobutan-1-ol



[0953] A mixture of (*cis*)-3-(5-bromo-2-methyl-7-(trifluoromethyl)-1H-benzo[d]imidazole-1-yl)-1-methylcyclobutan-1-ol (2.00 g, 5.51 mmol), 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5,5-dimethyl-1,3,2-dioxaborinane (2.49 g, 11.0 mmol), Pd(dppf)Cl_2 (403 mg, 551 μmol) and KOAc (1.62 g, 16.5 mmol) in 1,4-dioxane (30 mL) was degassed and purged with N_2 (3x), and then the mixture was stirred at 95 °C for 16 h under N_2 atmosphere. After cooling to room temperature, the mixture was diluted with H_2O (30 mL) and extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 40 g cartridge, 70–85% EtOAc/Petroleum ether) to give (*cis*)-3-(5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-2-methyl-7-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)-1-methylcyclobutan-1-ol. MS = 329.1 $[M–C_5H_8+H]^+$.

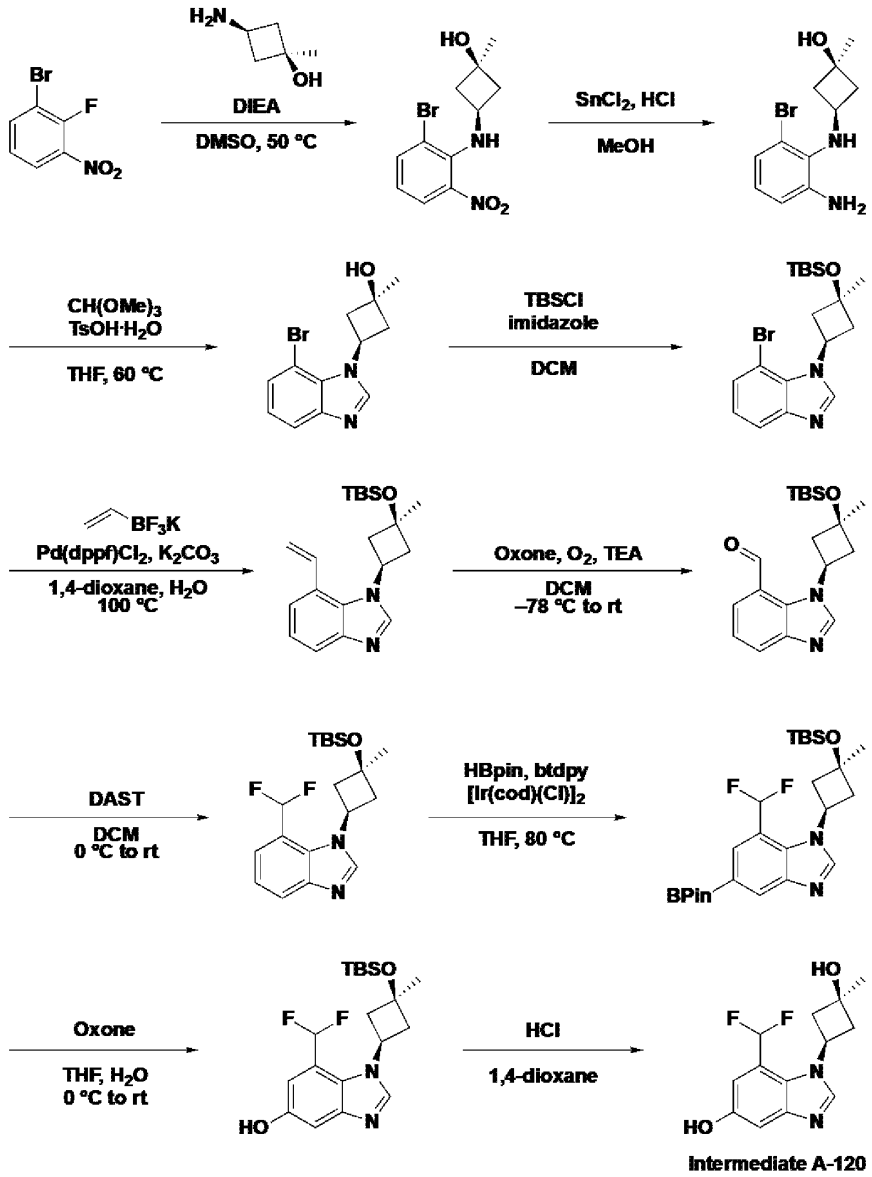
Step 3: 1-((*cis*)-3-hydroxy-3-methylcyclobutyl)-2-methyl-7-(trifluoromethyl)-1H-benzo[d]imidazol-5-ol



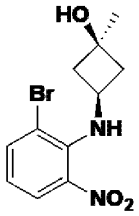
[0954] To a solution of (*cis*)-3-(5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-2-methyl-7-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)-1-methylcyclobutan-1-ol (2.00 g, 6.10 mmol) in THF (30 mL) and H_2O (10 mL) was added Oxone (3.75 g, 6.10 mmol). The mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with saturated aqueous Na_2SO_3 solution (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 40 g cartridge, 0–100% EtOAc/Petroleum

ether) to give 1-((*cis*)-3-hydroxy-3-methylcyclobutyl)-2-methyl-7-(trifluoromethyl)-1H-benzo[d]imidazole-5-ol (**Intermediate A-119**). MS = 301.1 $[M+H]^+$.

General Procedure for Intermediate A-120

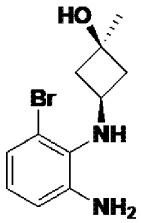


Step 1: (*cis*)-3-((2-bromo-6-nitrophenyl)amino)-1-methylcyclobutan-1-ol



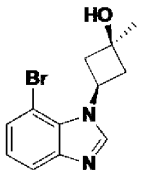
[0955] To a solution of 1-bromo-2-fluoro-3-nitro-benzene (11.0 g, 50.0 mmol) and (*cis*)-3-amino-1-methylcyclobutan-1-ol (8.26 g, 60.0 mmol, HCl salt) in DMSO (60 mL) was added DIEA (34.9 mL, 200 mmol). The mixture was stirred at 50 °C for 2 h. The reaction mixture was then quenched by addition of H_2O (150 mL) and extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with H_2O (3 x 100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give (*cis*)-3-[(2-bromo-6-nitrophenyl)amino]-1-methylcyclobutan-1-ol, which was taken to the next step without further purification. MS =301.1 / 303.1 $[M+H]^+$.

Step 2: (*cis*)-3-((2-amino-6-bromophenyl)amino)-1-methylcyclobutan-1-ol



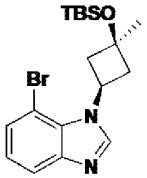
[0956] To a solution of (*cis*)-3-[(2-bromo-6-nitrophenyl)amino]-1-methylcyclobutan-1-ol (16.4 g, 54.5 mmol) in MeOH (120 mL) and 12 M aqueous HCl (30 mL, 360 mmol) was added $SnCl_2$ (31.0 g, 163 mmol). The mixture was stirred at room temperature for 2 h. The reaction mixture was adjusted to pH = 8 with 10% aqueous NaOH solution and then extracted with EtOAc (3 x 250 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 120 g cartridge, 0–45% EtOAc/Petroleum ether) to give (*cis*)-3-[(2-amino-6-bromophenyl)amino]-1-methylcyclobutan-1-ol. MS = 271.2 / 273.2 $[M+H]^+$.

Step 3: (*cis*)-3-(7-bromo-1H-1,3-benzodiazol-1-yl)-1-methylcyclobutan-1-ol



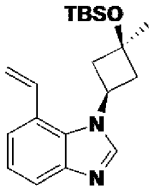
[0957] To a solution of (*cis*)-3-[(2-amino-6-bromophenyl)amino]-1-methylcyclobutan-1-ol (13.8 g, 50.7 mmol) in THF (130 mL) was added TsOH•H_2O (1.93 g, 10.1 mmol) and trimethyl orthoformate (11.0 mL, 101 mmol). The mixture was stirred at 60 °C for 2 h. After cooling to room temperature, the reaction mixture was quenched by addition of H_2O (300 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 x 200 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was triturated with MTBE (40 mL), then the filter cake was isolated by filtration and dried in vacuo to give (*cis*)-3-(7-bromo-1H-1,3-benzodiazol-1-yl)-1-methylcyclobutan-1-ol. MS = 281.2 / 283.2 $[M+H]^+$.

Step 4: 7-bromo-1-[(*cis*)-3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl]-1H-1,3-benzodiazole



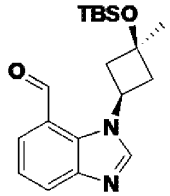
[0958] To a solution of (*cis*)-3-(7-bromo-1H-1,3-benzodiazol-1-yl)-1-methylcyclobutan-1-ol (12.5 g, 44.4 mmol) in DCM (150 mL) was added TBSCl (20.1 g, 133 mmol) and imidazole (18.2 g, 267 mmol). The mixture was stirred at room temperature for 16 h. The reaction mixture was quenched by addition of H_2O (200 mL), and then extracted with DCM (2 x 200 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (2 x 200 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 120 g cartridge, 0–8% EtOAc/Petroleum ether) to give 7-bromo-1-[(*cis*)-3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl]-1H-1,3-benzodiazole. MS = 395.3 / 397.3. $[M+H]^+$.

Step 5: 7-ethenyl-1-[(*cis*)-3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl]-1H-1,3-benzodiazole



[0959] A mixture of 7-bromo-1-[(*cis*)-3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl]-1H-1,3-benzodiazole (16.9 g, 42.7 mmol), potassium vinyltrifluoroborate (17.2 g, 128 mmol), K_2CO_3 (17.7 g, 128 mmol) and $Pd(dppf)Cl_2$ (3.13 g, 4.27 mmol) in 1,4-dioxane (140 mL) and H_2O (35 mL) was degassed and purged with N_2 (3x), and then the mixture was stirred at 100 °C for 16 h under N_2 atmosphere. The reaction mixture was concentrated in vacuo, then was diluted with H_2O (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (2 x 200 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 220 g cartridge, 0–20% EtOAc/Petroleum ether) to give 7-ethenyl-1-[(*cis*)-3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl]-1H-1,3-benzodiazole. MS = 343.2 $[M+H]^+$.

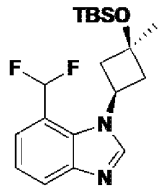
Step 6: 1-[(*cis*)-3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl]-1H-1,3-benzodiazole-7-carbaldehyde



[0960] Ozone was bubbled into a –78 °C solution of 7-ethenyl-1-[(*cis*)-3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl]-1H-1,3-benzodiazole (3.00 g, 8.76 mmol) in DCM (40 mL) for 20 min. The resulting solution was then purged with O_2 for an additional 10 min before being treated with TEA (886 mg, 8.76 mmol), and then the mixture was allowed to warm to room temperature for 10 min. The reaction mixture was adjusted to pH = 5 with 3.0 M aqueous HCl solution, and then extracted with DCM (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 40 g cartridge, 0–15% EtOAc/Petroleum ether) to give 1-[(*cis*)-3-[(*tert*-

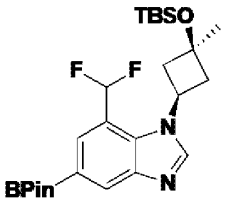
butyldimethylsilyl)oxy]-3-methylcyclobutyl]-1H-1,3-benzodiazole-7-carbaldehyde. MS = 345.3. $[M+H]^+$.

Step 7: 7-(difluoromethyl)-1-[(*cis*)-3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl]-1H-1,3-benzodiazole



[0961] To a 0 °C solution of 1-[(*cis*)-3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl]-1H-1,3-benzodiazole-7-carbaldehyde (2.54 g, 7.37 mmol) in DCM (30 mL) was added DAST (4.16 g, 25.8 mmol). The mixture was stirred at room temperature for 16 h. The reaction mixture was cooled to 0 °C, quenched by addition of H_2O (50 mL), and then extracted with DCM (2 x 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (3 x 50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 40 g cartridge, 0–15% EtOAc/Petroleum ether) to give 7-(difluoromethyl)-1-[(*cis*)-3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl]-1H-1,3-benzodiazole. MS = 367.3 $[M+H]^+$.

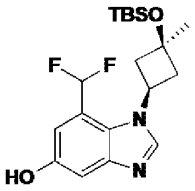
Step 8: 7-(difluoromethyl)-1-[(*cis*)-3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-1,3-benzodiazole



[0962] To a solution of 7-(difluoromethyl)-1-[(*cis*)-3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl]-1H-1,3-benzodiazole (500 mg, 1.36 mmol) in THF (10 mL) was added pinacolborane (2.62 g, 20.5 mmol), 4,4'-di-*tert*-butyl-2,2'-dipyridyl (73.2 mg, 273 μmol) and (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (91.6 mg, 136 μmol). The mixture was degassed and purged with N_2 (3x), and then stirred at 80 °C for 32 h. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated in vacuo to give 7-(difluoromethyl)-1-[(*cis*)-3-

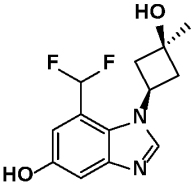
[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-1,3-benzodiazole, which was taken to the next step without further purification. MS = 493.2 $[M+H]^+$.

Step 9: 7-(difluoromethyl)-1-[(*cis*)-3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-ol



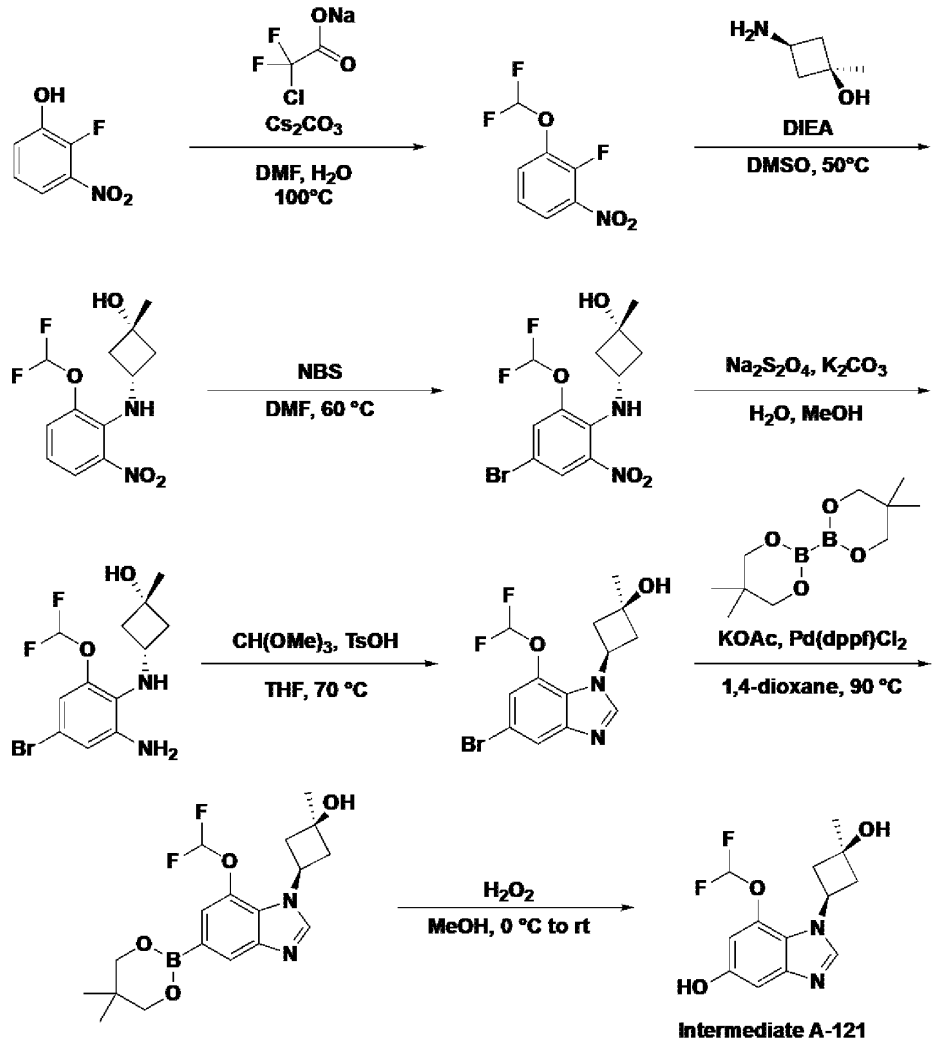
[0963] To a 0 °C solution of 7-(difluoromethyl)-1-[(*cis*)-3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-1,3-benzodiazole (700 mg, 1.42 mmol) in H_2O (5 mL) and THF (5 mL) was added Oxone (1.31 g, 2.13 mmol). The mixture was then stirred at room temperature for 2 h. The reaction mixture was quenched by addition of saturated aqueous Na_2SO_3 solution (100 mL) and then extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase preparative HPLC (Phenomenex Luna C_{18} column, 40–70% MeCN:10 mM TFA in H_2O) to give 7-(difluoromethyl)-1-[(*cis*)-3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-ol. MS = 383.2 $[M+H]^+$.

Step 10: 7-(difluoromethyl)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-ol

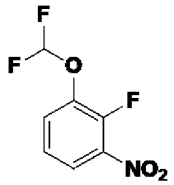


[0964] To a solution of 7-(difluoromethyl)-1-[(*cis*)-3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-ol (50.0 mg, 65.4 μmol) in 1,4-dioxane (0.5 mL) was added 4.0 M HCl in 1,4-dioxane (2.0 mL, 8.0 mmol). The mixture was stirred at room temperature for 2 h, then was concentrated in vacuo to give 7-(difluoromethyl)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-ol (**Intermediate A-120**), which was taken to the next step without further purification. MS = 269.1 $[M+H]^+$.

General Procedure for Intermediate A-121



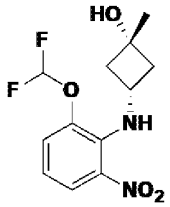
Step 1: 1-(difluoromethoxy)-2-fluoro-3-nitro-benzene



[0965] To a mixture of 2-fluoro-3-nitro-phenol (2.00 g, 12.7 mmol) and Cs_2CO_3 (12.4 g, 38.2 mmol) in DMF (20 mL) and H_2O (4 mL) was added sodium chlorodifluoroacetate (19.4 g, 127

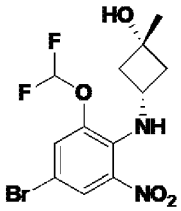
mmol). The mixture was stirred at 100 °C for 6 h. After cooling to room temperature, the reaction mixture was quenched by addition of H_2O (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (2 x 30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 20 g cartridge, 0–15% EtOAc/Petroleum ether) to give 1-(difluoromethoxy)-2-fluoro-3-nitro-benzene. MS = 208.0 $[M+H]^+$.

Step 2: (*cis*)-3-{[2-(difluoromethoxy)-6-nitrophenyl]amino}-1-methylcyclobutan-1-ol



[0966] To a solution of 1-(difluoromethoxy)-2-fluoro-3-nitro-benzene (1.20 g, 5.79 mmol) in DMSO (12 mL) was added DIEA (3.00 g, 23.2 mmol) and (*cis*)-3-amino-1-methylcyclobutan-1-ol (877 mg, 6.37 mmol, HCl salt). The mixture was stirred at 50 °C for 2 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3 x 5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give (*cis*)-3-{[2-(difluoromethoxy)-6-nitrophenyl]amino}-1-methylcyclobutan-1-ol, which was taken to the next step without further purification. MS = 288.9 $[M+H]^+$.

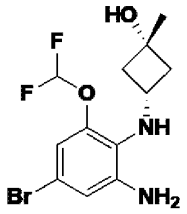
Step 3: (*cis*)-3-{[4-bromo-2-(difluoromethoxy)-6-nitrophenyl]amino}-1-methylcyclobutan-1-ol



[0967] To a solution of (*cis*)-3-{[2-(difluoromethoxy)-6-nitrophenyl]amino}-1-methylcyclobutan-1-ol (1.80 g, 6.24 mmol) in DMF (40 mL) was added NBS (2.22 g, 12.5 mmol). The mixture was stirred at 60 °C for 12 h. After cooling to room temperature, the reaction mixture was quenched by addition of H_2O (120 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered, and concentrated in

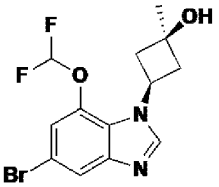
vacuo. The residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–15% EtOAc/Petroleum ether) to give (*cis*)-3-{[4-bromo-2-(difluoromethoxy)-6-nitrophenyl]amino}-1-methylcyclobutan-1-ol. MS = 367.0 / 369.0 $[M+H]^+$.

Step 4: (*cis*)-3-{[2-amino-4-bromo-6-(difluoromethoxy)phenyl]amino}-1-methylcyclobutan-1-ol



[0968] To a solution of K_2CO_3 (1.88 g, 13.6 mmol) in H_2O (5 mL) was added $Na_2S_2O_4$ (1.42 g, 8.17 mmol) followed by (*cis*)-3-{[4-bromo-2-(difluoromethoxy)-6-nitrophenyl]amino}-1-methylcyclobutan-1-ol (1.00 g, 2.72 mmol) in MeOH (5 mL). The mixture was stirred at room temperature for 1 h. The reaction mixture was quenched by addition of H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give (*cis*)-3-{[2-amino-4-bromo-6-(difluoromethoxy)phenyl]amino}-1-methylcyclobutan-1-ol, which was taken to the next step without further purification. MS = 337.0 / 339.0 $[M+H]^+$.

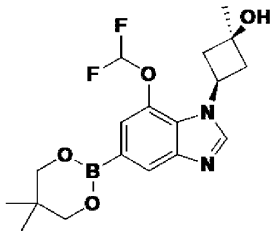
Step 5: (*cis*)-3-[5-bromo-7-(difluoromethoxy)-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol



[0969] To a solution of (*cis*)-3-{[2-amino-4-bromo-6-(difluoromethoxy)phenyl]amino}-1-methylcyclobutan-1-ol (720 mg, 2.14 mmol) in THF (11 mL) was added $TsOH•H_2O$ (81.2 mg, 427 μmol) and trimethyl orthoformate (453 mg, 4.27 mmol). The mixture was stirred at 70 °C for 2 h. After cooling to room temperature, the reaction mixture was quenched by addition of H_2O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting solid was triturated with MTBE (20 mL) for 10 min, then the filter cake was isolated by filtration and dried in vacuo to give

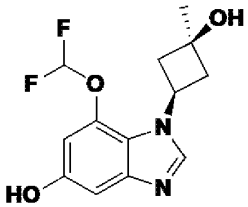
(*cis*)-3-[5-bromo-7-(difluoromethoxy)-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol, which was taken to the next step without further purification. MS = 347.0 / 348.9 $[M+H]^+$.

Step 6: (*cis*)-3-[7-(difluoromethoxy)-5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol



[0970] A mixture of (*cis*)-3-[5-bromo-7-(difluoromethoxy)-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol (1.50 g, 4.32 mmol), 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5,5-dimethyl-1,3,2-dioxaborinane (2.93 g, 12.9 mmol), KOAc (1.06 g, 10.8 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (353 mg, 432 μmol) in 1,4-dioxane (25 mL) was degassed and purged with N_2 (3x), and then the mixture was stirred at 90 °C for 12 h under N_2 atmosphere. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo to give (*cis*)-3-[7-(difluoromethoxy)-5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol, which was taken to the next step without further purification. MS = 313.1 $[M–C_5H_8+H]^+$.

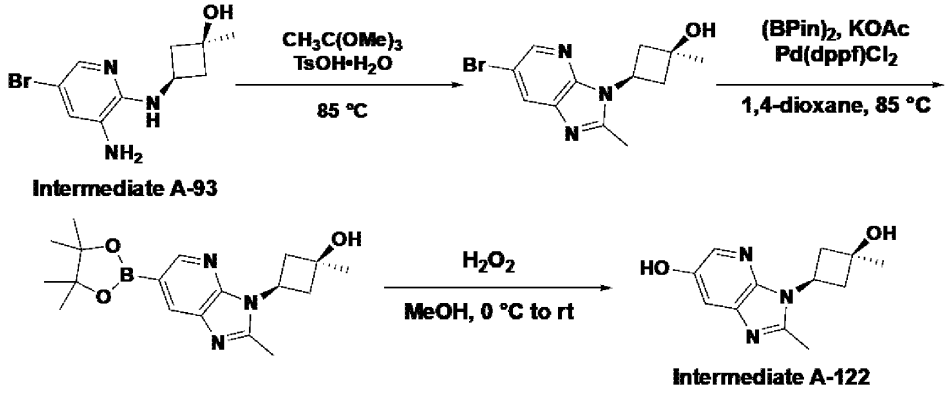
Step 7: 7-(difluoromethoxy)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-ol



[0971] To a 0 °C solution of (*cis*)-3-[7-(difluoromethoxy)-5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol (2.00 g, 5.26 mmol) in MeOH (25 mL) was added dropwise 30% H_2O_2 in H_2O (10.2 mL, 106 mmol). The resulting mixture was then stirred at room temperature for 1 h. The mixture was quenched with saturated aqueous Na_2SO_3 solution (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 filtered and concentrated in vacuo to give 7-(difluoromethoxy)-1-[(*cis*)-3-hydroxy-3-

methylcyclobutyl]-1H-1,3-benzodiazol-5-ol (**Intermediate A-121**), which was taken to the next step without further purification. MS = 285.1 $[M+H]^+$.

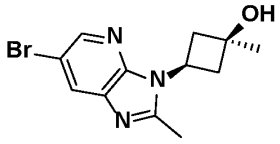
General Procedure for Intermediate A-122



Intermediate A-93

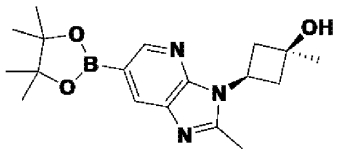
Intermediate A-122

Step 1: (*cis*)-3-{6-bromo-2-methyl-3H-imidazo[4,5-b]pyridin-3-yl}-1-methylcyclobutan-1-ol



[0972] A mixture of (*cis*)-3-[(3-amino-5-bromopyridin-2-yl)amino]-1-methylcyclobutan-1-ol (**Intermediate A-93**, 630 mg, 2.32 mmol), *p*TSA•H_2O (220 mg, 1.16 mmol) and triethyl orthoacetate (5.89 mL, 46.3 mmol) was stirred at 85 °C for 2 h. The mixture was cooled to room temperature, then diluted with H_2O (20 mL), and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel chromatography (Biotage 50 g cartridge, 0–100% EtOAc/hexane) to give (*cis*)-3-{6-bromo-2-methylimidazo[4,5-b]pyridin-3-yl}-1-methylcyclobutan-1-ol. MS = 296.2 / 298.2 $[M+H]^+$.

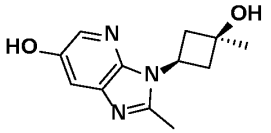
Step 2: (*cis*)-1-methyl-3-[2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3H-imidazo[4,5-b]pyridin-3-yl]cyclobutan-1-ol



[0973] A mixture of (*cis*)-3-{6-bromo-2-methylimidazo[4,5-b]pyridin-3-yl}-1-methylcyclobutan-1-ol (250 mg, 0.844 mmol), bis(pinacolato)diboron (257 mg, 1.01 mmol.),

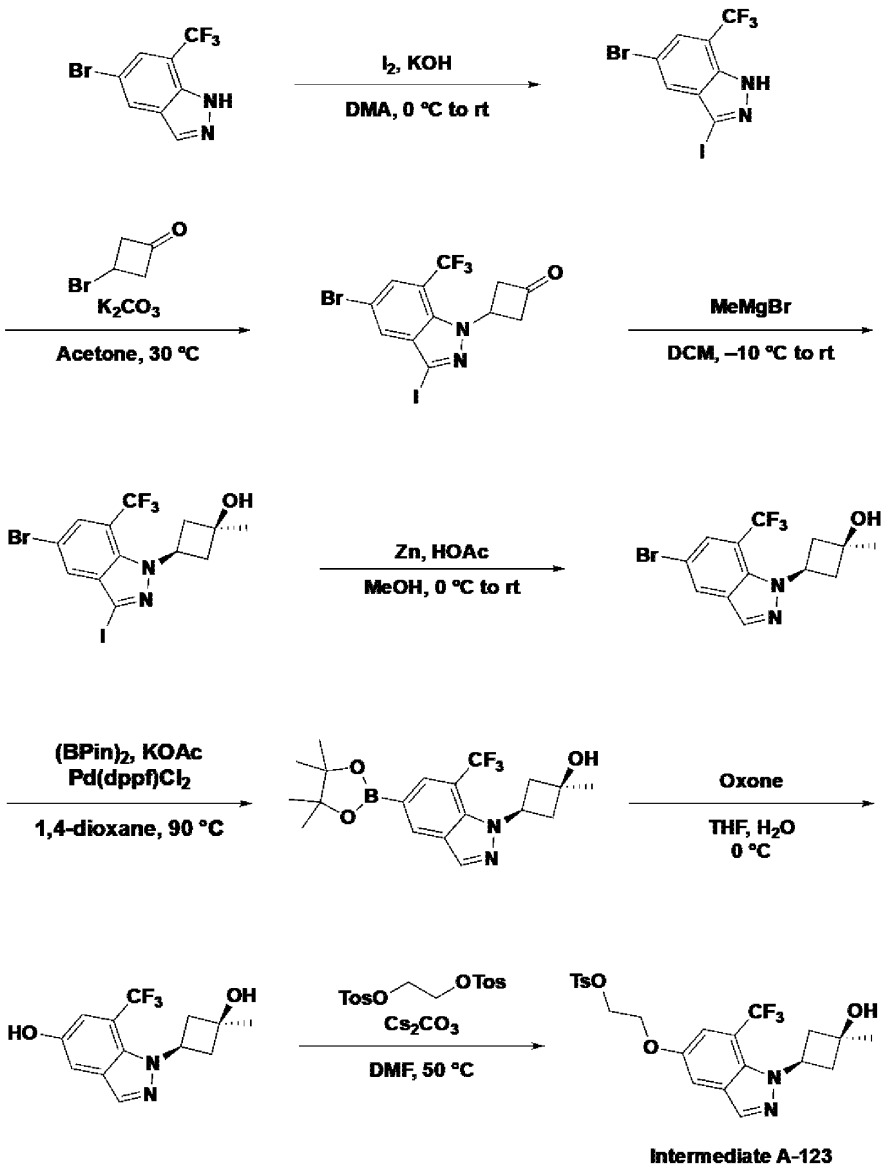
$Pd(dppf)Cl_2•CH_2Cl_2$ (34 mg, 0.042 mmol) and KOAc (166 mg, 1.69 mmol) in 1,4-dioxane (8 mL) was purged with nitrogen for 10 min at room temperature, then stirred at 85 °C for 16 h. The reaction mixture was cooled to room temperature and filtered through a Celite pad. The filtrate was concentrated in vacuo to give (*cis*)-1-methyl-3-[2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[4,5-b]pyridin-3-yl]cyclobutan-1-ol, which was taken to the next step without further purification. MS = 344.0 $[M+H]^+$.

Step 3: 2-methyl-3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-3H-imidazo[4,5-b]pyridin-6-ol

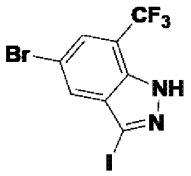


[0974] To a mixture of (*cis*)-1-methyl-3-[2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[4,5-b]pyridin-3-yl]cyclobutan-1-ol (0.290 g, 0.844 mmol) in MeOH (4 mL) at 0 °C was added 30% H_2O_2 in H_2O (0.216 mL, 2.11 mmol) dropwise. The mixture was warmed to room temperature and stirred for 2 h. The mixture was then concentrated in vacuo to give 2-methyl-3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]imidazo[4,5-b]pyridin-6-ol (**Intermediate A-122**) , which was taken to the next step without further purification. MS = 234.2 $[M+H]^+$.

General Procedure for Intermediate A-123

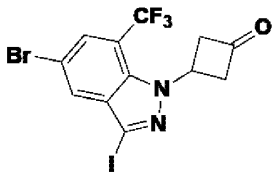


Step 1: 5-bromo-3-iodo-7-(trifluoromethyl)-1H-indazole



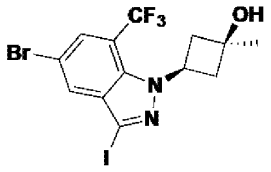
[0975] To a 0 °C solution of 5-bromo-7-(trifluoromethyl)-1H-indazole (4.50 g, 17.0 mmol) in DMA (40 mL) was added I_2 (3.42 mL, 17.0 mmol) and KOH (2.86 g, 50.9 mmol). The mixture was stirred at room temperature for 6 h. The mixture was diluted with H_2O (40 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage, 40 g cartridge, 0–25% EtOAc/Petroleum ether) to give 5-bromo-3-iodo-7-(trifluoromethyl)-1H-indazole. MS = 390.6 / 392.6 $[M+H]^+$.

Step 2: 3-[5-bromo-3-iodo-7-(trifluoromethyl)-1H-indazol-1-yl]cyclobutan-1-one



[0976] To a solution of 5-bromo-3-iodo-7-(trifluoromethyl)-1H-indazole (3.40 g, 8.70 mmol) in acetone (30 mL) was added K_2CO_3 (3.61 g, 26.1 mmol) and 3-bromocyclobutanone (3.89 g, 26.1 mmol). The mixture was stirred at 30 °C for 12 h. The mixture was diluted with H_2O (30 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 20 g cartridge, 0–20% EtOAc/Petroleum ether) to provide 3-(5-bromo-3-iodo-7-(trifluoromethyl)-1H-indazol-1-yl)cyclobutan-1-one as the first eluting isomer. MS = 458.7 / 460.6 $[M+H]^+$.

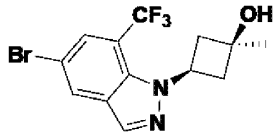
Step 3: (*cis*)-3-[5-bromo-3-iodo-7-(trifluoromethyl)-1H-indazol-1-yl]-1-methylcyclobutan-1-ol



[0977] To a –10 °C solution of 3-(5-bromo-3-iodo-7-(trifluoromethyl)-1H-indazol-1-yl)cyclobutan-1-one (1.20 g, 2.62 mmol) in DCM (20 mL) under N_2 atmosphere was added 3.0 M MeMgBr in 2-Me-THF (871 µL, 2.62 mmol). The mixture was stirred at room temperature for 1 h under N_2 atmosphere. The reaction mixture was cooled to 0 °C and quenched by addition of H_2O (5 mL), and then extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel

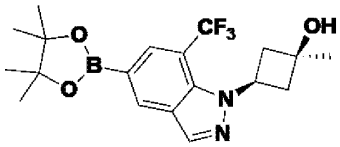
chromatography (Isco 20 g cartridge, 0–8% EtOAc/Petroleum ether) to provide (*cis*)-3-[5-bromo-3-iodo-7-(trifluoromethyl)-1H-indazol-1-yl]-1-methylcyclobutan-1-ol. MS = 474.9 / 476.9 $[M+H]^+$.

Step 4: (*cis*)-3-[5-bromo-7-(trifluoromethyl)-1H-indazol-1-yl]-1-methylcyclobutan-1-ol



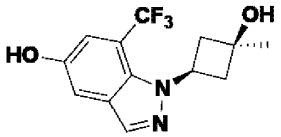
[0978] To a 0 °C mixture of (*cis*)-3-(5-bromo-3-iodo-7-(trifluoromethyl)-1H-indazol-1-yl)-1-methylcyclobutan-1-ol (650 mg, 1.37 mmol) in HOAc (7 mL) and MeOH (7 mL) was added Zn (930 mg, 14.2 mmol) portion wise. The mixture was stirred at 0 °C for 30 min, then allowed to warm to room temperature and stirred for another 30 min. The mixture was filtered, and the filtrate was poured into H_2O (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (SepaFlash 20 g cartridge, 0–20% EtOAc/Petroleum ether) to provide (*cis*)-3-[5-bromo-7-(trifluoromethyl)-1H-indazol-1-yl]-1-methylcyclobutan-1-ol. MS = 348.9 / 350.9 $[M+H]^+$.

Step 5: (*cis*)-1-methyl-3-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-(trifluoromethyl)-1H-indazol-1-yl]cyclobutan-1-ol



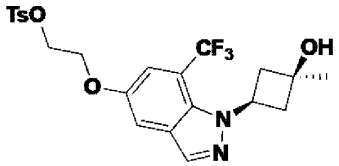
[0979] A mixture of (*cis*)-3-[5-bromo-7-(trifluoromethyl)-1H-indazol-1-yl]-1-methylcyclobutan-1-ol (380 mg, 1.09 mmol), bis(pinacolato)diboron (553 mg, 2.18 mmol), Pd(dppf)Cl_2 (79.6 mg, 109 μmol), and KOAc (320 mg, 3.27 mmol) in 1,4-dioxane (10 mL) was degassed and purged with N_2 (3x), and then the mixture was stirred at 90 °C for 2 h under N_2 atmosphere. After cooling to room temperature, the mixture was filtered, and the filtrate was concentrated in vacuo to give (*cis*)-1-methyl-3-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-(trifluoromethyl)-1H-indazol-1-yl]cyclobutan-1-ol. MS = 397.1 $[M+H]^+$.

Step 6: 1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-indazol-5-ol



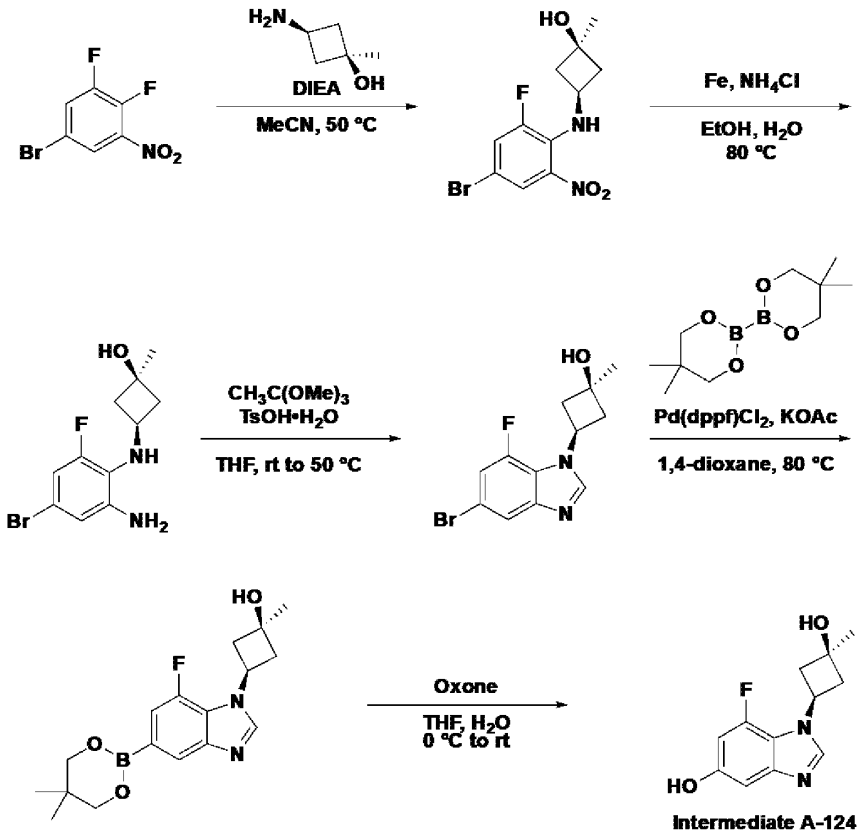
[0980] A 0 °C mixture of (*cis*)-1-methyl-3-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-(trifluoromethyl)-1H-indazol-1-yl]cyclobutan-1-ol (431 mg, 1.09 mmol) and Oxone (1.34 g, 2.18 mmol) in THF (10 mL) and H_2O (10 mL) was stirred for 1 h. The 0 °C mixture was quenched with saturated aqueous Na_2SO_3 solution (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide 1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-indazol-5-ol, which was used in the subsequent step without further purification. MS = 287.1 $[M+H]^+$.

Step 7: 2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-indazol-5-yl}oxy)ethyl 4-methylbenzene-1-sulfonate



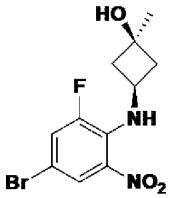
[0981] A mixture of 1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-indazol-5-ol (250 mg, 873 μmol), 1,2-bis(tosyloxy)ethane (1.29 g, 3.49 mmol) and Cs_2CO_3 (854 mg, 2.62 mmol) in DMF (12 mL) was stirred at 50 °C for 4 h. After cooling to room temperature, the reaction was quenched with ice water (30 mL) and extracted with EtOAc (2 x 40 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (SepaFlash 20 g cartridge, 0–60% EtOAc/Petroleum ether) to provide 2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-indazol-5-yl}oxy)ethyl 4-methylbenzene-1-sulfonate (**Intermediate A-123**). MS = 485.0 $[M+H]^+$.

General Procedure for Intermediate A-124



Intermediate A-124

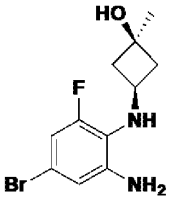
Step 1: (*cis*)-3-[(4-bromo-2-fluoro-6-nitrophenyl)amino]-1-methylcyclobutan-1-ol



[0982] To a solution of 5-bromo-1,2-difluoro-3-nitro-benzene (12.0 g, 50.4 mmol) in MeCN (120 mL) was added (*cis*)-3-amino-1-methylcyclobutan-1-ol (6.94 g, 50.4 mmol, HCl salt) and DIEA (26.4 mL, 151 mmol). The mixture was stirred at 50 °C for 12 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo. The residue was diluted with H_2O (60 mL) and extracted with EtOAc (4 x 80 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Sepaflash 120 g cartridge, 0–15% EtOAc/Petroleum

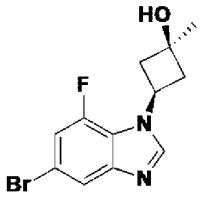
ether) to provide (*cis*)-3-[(4-bromo-2-fluoro-6-nitrophenyl)amino]-1-methylcyclobutan-1-ol. MS = 319.0 / 320.9 $[M+H]^+$.

Step 2: (*cis*)-3-[(2-amino-4-bromo-6-fluorophenyl)amino]-1-methylcyclobutan-1-ol



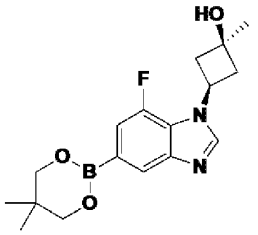
[0983] To a solution of (*cis*)-3-[(4-bromo-2-fluoro-6-nitrophenyl)amino]-1-methylcyclobutan-1-ol (2.00 g, 6.27 mmol) in EtOH (20 mL) and H_2O (10 mL) was added Fe (1.05 g, 18.8 mmol) and NH_4Cl (1.68 g, 31.3 mmol). The mixture was stirred at 80 °C for 2 h. After cooling to room temperature, solids were removed by filtration and the filtrate was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Sepaflash 40 g cartridge, 0–10% EtOAc/Petroleum ether) to provide (*cis*)-3-[(2-amino-4-bromo-6-fluorophenyl)amino]-1-methylcyclobutan-1-ol. MS = 289.1 / 291.1 $[M+H]^+$.

Step 3: (*cis*)-3-(5-bromo-7-fluoro-1H-1,3-benzodiazol-1-yl)-1-methylcyclobutan-1-ol



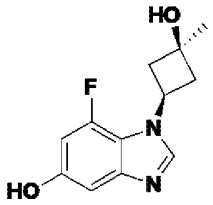
[0984] To a solution of trimethyl orthoformate (2.27 mL, 20.8 mmol) and (*cis*)-3-[(2-amino-4-bromo-6-fluorophenyl)amino]-1-methylcyclobutan-1-ol (5.00 g, 17.3 mmol) in THF (50 mL) was added $TsOH•H_2O$ (329 mg, 1.73 mmol). After slowly warming to 50 °C, the mixture was stirred at 50 °C for 5 h. The reaction mixture was cooled to room temperature, quenched with H_2O (30 mL), and adjusted to pH = 8 by dropwise addition of saturated aqueous $NaHCO_3$ solution. The mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give (*cis*)-3-(5-bromo-7-fluoro-1H-1,3-benzodiazol-1-yl)-1-methylcyclobutan-1-ol, which was used in the subsequent step without further purification. MS = 299.0 / 301.1 $[M+H]^+$.

Step 4: (*cis*)-3-[5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-7-fluoro-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol



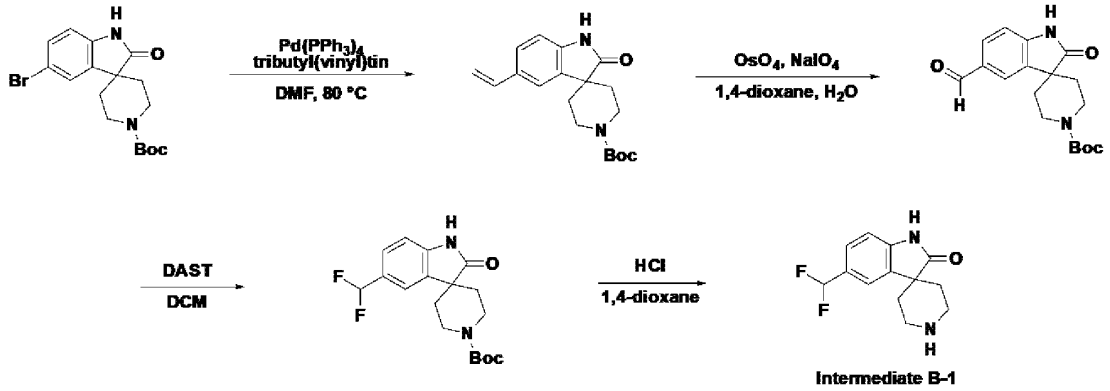
[0985] To a solution of (*cis*)-3-(5-bromo-7-fluoro-1H-benzo[d]imidazol-1-yl)-1-methylcyclobutan-1-ol (4.00 g, 13.4 mmol) and 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5,5-dimethyl-1,3,2-dioxaborinane (3.62 g, 16.1 mmol) in 1,4-dioxane (60 mL) under N_2 atmosphere was added KOAc (3.28 g, 33.4 mmol) and Pd(dppf)Cl_2 (978 mg, 1.34 mmol). The mixture was stirred at 80 °C for 16 h under N_2 atmosphere. The reaction mixture was allowed to cool to room temperature, then solids were removed by filtration and the filtrate was concentrated in vacuo to give (*cis*)-3-[5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-7-fluoro-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol, which was used in the subsequent step without further purification. MS = 333.1 $[M+H]^+$.

Step 5: 7-fluoro-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-ol

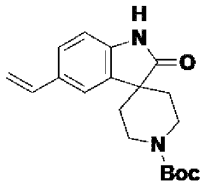


[0986] To a 0 °C solution of (*cis*)-3-[5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-7-fluoro-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol (3.00 g, 9.03 mmol) and H_2O (10 mL) in THF (30 mL) was added Oxone (2.78 g, 4.52 mmol) portion wise, and then the mixture was stirred at room temperature for 2 h. The reaction mixture was cooled to 0 °C then quenched by addition of saturated aqueous Na_2SO_3 solution (30 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give 7-fluoro-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-ol (**Intermediate A-124**). MS = 237.2 $[M+H]^+$.

General Procedure for Intermediate B-1

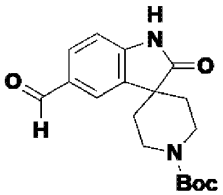


Step 1: *tert*-Butyl 5-ethenyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate



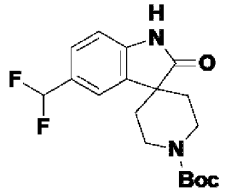
[0987] To a solution of *tert*-butyl 5-bromo-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (555 mg, 1.45 mmol) in DMF (7.3 mL) was added tributyl(vinyl)tin (640 µL, 2.2 mmol). The mixture was sparged with N_2 for 10 min and tetrakis(triphenylphosphine)palladium (168 mg, 0.15 mmol) was added. The reaction mixture was flushed with N_2, sealed, and heated to 80 °C. After 16 h the reaction mixture was removed from heat and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 25 g cartridge, 0–100% EtOAc:hexanes) to afford *tert*-butyl 5-ethenyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.93 (s, 1H), 7.39 (s, 1H), 7.31 (d, J = 8.0, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.72 (dd, J = 17.5, 10.8 Hz, 1H), 5.69 (d, J = 17.6 Hz, 1H), 5.22 (d, J = 10.9 Hz, 1H), 3.98–3.74 (m, 4H), 1.99–1.78 (m, 4H), 1.56 (s, 9H).

Step 2: *tert*-Butyl 5-formyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate



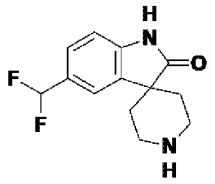
[0988] To a solution of *tert*-butyl 5-ethenyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (311 mg, 0.95 mmol) in 1,4-dioxane (8 mL) and water (4.5 mL) was added sodium periodate (405 mg, 1.89 mmol) followed by OsO_4 (500 µL, 2.5% w/w in *t*-BuOH, 0.38 mmol). The reaction mixture was stirred for 3 h at room temperature and then diluted with EtOAc (30 mL) and quenched with saturated aqueous Na_2SO_3 (50 mL). The aqueous layer was then extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by normal phase silica gel chromatography (Biotage 25 g cartridge, 80% EtOAc:hexanes) afforded *tert*-butyl 5-formyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.93 (s, 1H), 8.34 (br s, 1H), 7.86 (s, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 3.86 (dd, J = 6.7, 4.9 Hz, 4H), 1.98–1.71 (m, 4H), 1.54 (s, 9H). MS = 231.1 $[M–C_4H_8+H]^+$.

Step 3: *tert*-Butyl 5-(difluoromethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate



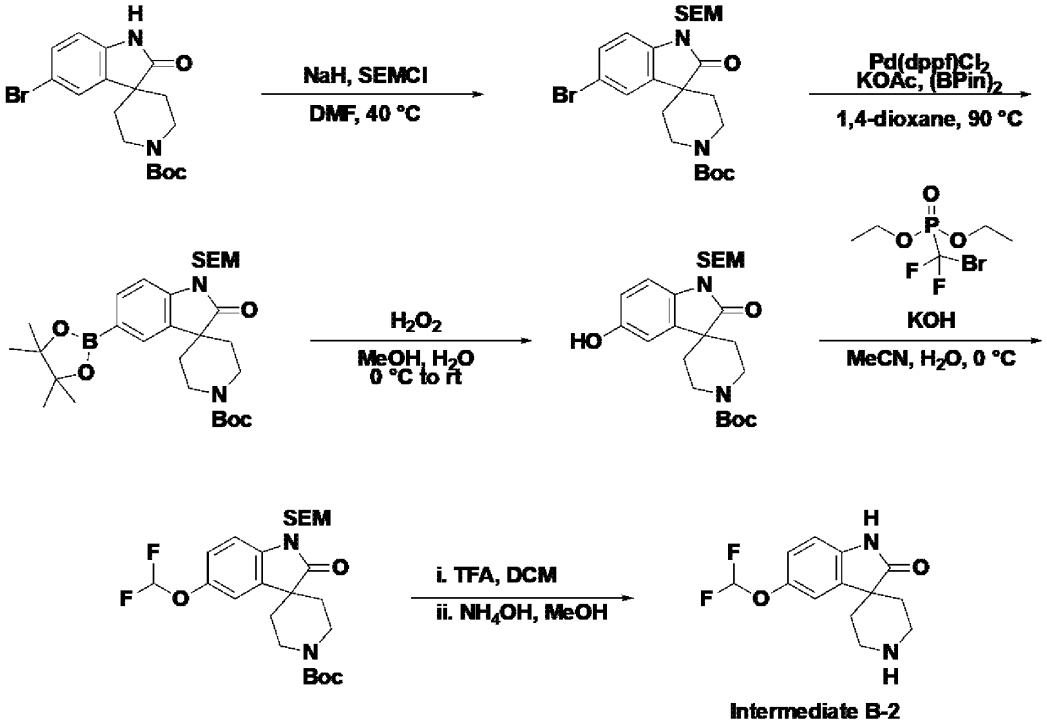
[0989] To a solution of *tert*-butyl 5-formyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (71.0 mg, 0.215 mmol) in DCM (1.4 mL) was added DAST (85 µL, 0.64 mmol) and the reaction was stirred at room temperature 16 h. The reaction mixture was then quenched by the addition of saturated aqueous $NaHCO_3$. The reaction mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by normal phase silica gel chromatography (Biotage 10 g cartridge, 40% EtOAc:hexanes) to afford *tert*-butyl 5-(difluoromethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.35 (s, 1H), 7.32–7.30 (m, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.55 (t, J = 56.6 Hz, 1H), 3.76 (dd, J = 8.2, 4.3 Hz, 4H), 1.83–1.73 (m, 4H), 1.44 (s, 9H). MS = 297.0 $[M–C_4H_8+H]^+$.

Step 4: 5-(Difluoromethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

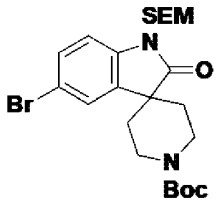


[0990] tert-Butyl 5-(difluoromethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (32 mg, 0.091 mmol) was dissolved in a 4.0 M HCl in dioxane solution (300 μL, 1.2 mmol) and stirred at room temperature for 1 h. The reaction mixture was then concentrated in vacuo to afford 5-(difluoromethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-1**), which was used without further purification. MS = 253.1 $[M+H]^+$.

General Procedure for Intermediate B-2

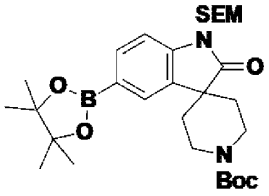


Step 1: *tert*-butyl 5-bromo-2-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate



[0991] To a solution of tert-butyl 5-bromo-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (1.55 g, 4.06 mmol) in DMF (21 mL) was added sodium hydride (195 mg, 60 wt% in mineral oil, 4.9 mmol). After one hour, SEMCl (935 µL, 5.3 mmol) was added dropwise over 30 sec and the reaction mixture was heated to 40 °C. After 48 h the reaction was removed from heat and diluted with EtOAc (50 mL) and quenched with H_2O (100 mL). The aqueous layer was then extracted with EtOAc (3 x 50 mL). The combined organic layers were then washed with brine (150 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude reaction mixture was the purified by normal phase chromatography (Biotage 50 g cartridge 20% EtOAc:hexanes) to afford tert-butyl 5-bromo-2-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (app d, J = 1.9 Hz, 2H), 7.02–6.96 (m, 1H), 5.17 (s, 2H), 3.85 (m, 4H), 3.69–3.44 (m, 2H), 2.00–1.74 (m, 4H), 1.55 (s, 9H), 1.05–0.82 (m, 2H), 0.00 (s, 9H).

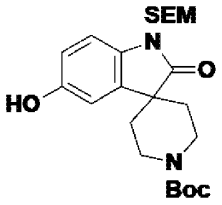
Step 2: *tert*-butyl 2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate



[0992] A solution tert-butyl 5-bromo-2-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (1.53 g, 3.1 mmol), KOAc (604 mg, 6.1 mmol), bis(pinacolato)diboron (937 mg, 2.2 mmol) in 1,4-dioxane (9.3 mL) was sparged with N_2 for 10 min. Pd(dppf)Cl_2 (113 mg, 0.15 mmol) was then added, and the reaction was heated to 90 °C for 2 h. The reaction mixture was then cooled to room temperature, filtered over Celite, washed with EtOAc (30 mL), and concentrated in vacuo. The crude material was then purified by normal phase chromatography (Biotage 25 g cartridge, 10% EtOAc:hexanes) to give tert-butyl 2-oxo-5-(4,4,5,5-

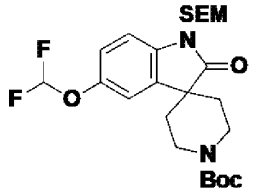
tetramethyl-1,3,2-dioxaborolan-2-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate.

Step 3. *Tert*-butyl 5-hydroxy-2-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate



[0993] tert-Butyl 5-hydroxy-2-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (3.1 mmol) was dissolved in MeOH (20.5 mL). The solution was cooled to 0 °C and 30% aqueous hydrogen peroxide solution (1.05 mL, 9.3 mmol) was added dropwise over 3 min. The reaction mixture was then warmed to room temperature and stirred for 16 h. The reaction mixture was then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase chromatography (Biotage 25 g cartridge, 40% EtOAc in hexanes) to afford tert-butyl 5-hydroxy-2-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate. ^{1}H NMR (500 MHz, $CDCl_3$, 35/36 H): δ 6.96 (d, J = 8.4 Hz, 1H), 6.91 (s, 1H), 6.82 (d, J = 8.4, 1H), 5.16 (s, 2H), 3.96–3.71 (m, 4H), 3.67–3.49 (m, 2H), 1.87–1.85 (m, 2H), 1.77–1.75 (m, 2H), 1.56 (s, 9H), 1.00–0.91 (m, 2H), 0.00 (s, 9H).

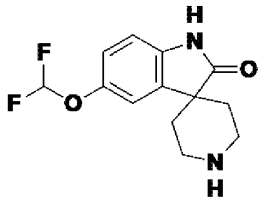
Step 4: *tert*-Butyl 5-(difluoromethoxy)-2-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate



[0994] A solution of tert-butyl 5-hydroxy-2-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (295 mg, 0.66 mmol) in MeCN (2 mL) and H_2O (2 mL) was cooled to 0 °C and KOH (738 mg, 13.1 mmol) was added. The mixture was stirred at 0 °C for 20 min, then diethyl bromodifluoromethyl phosphonate (316 mg, 1.18 mmol) was added.

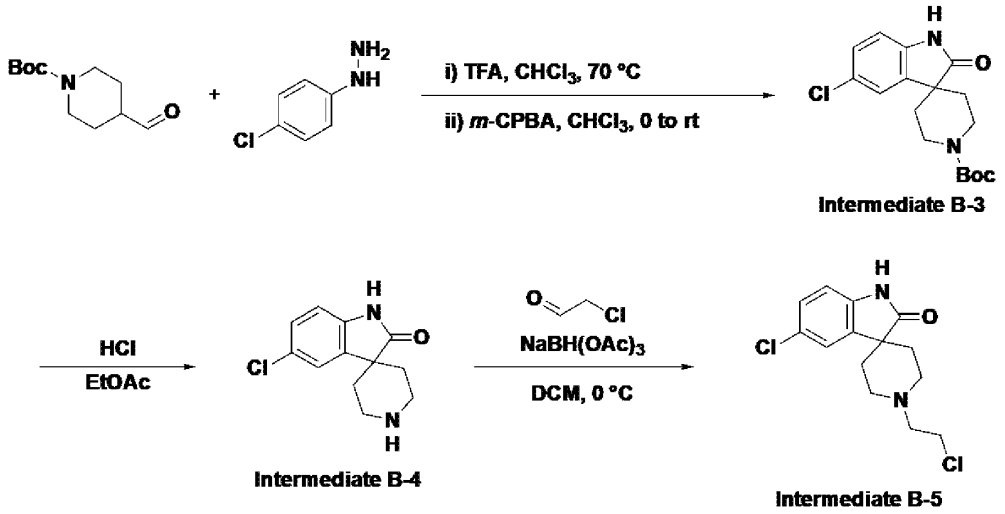
After 2 h, the reaction mixture was acidified to pH = 3 by addition of 1.0 M aqueous HCl. The reaction mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by normal phase chromatography (Biotage 10 g cartridge, 30% EtOAc:hexanes) gave tert-butyl 5-(difluoromethoxy)-2-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,2-dihydrospiro[indole-3,4''-piperidine]-1''-carboxylate. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17–7.04 (m, 3H), 6.50 (t, J = 73.8 Hz, 1H), 5.18 (s, 2H), 3.98–3.78 (m, 4H), 3.68–3.46 (m, 2H), 1.98–1.74 (m, 4H), 1.54 (s, 9H), 1.06–0.84 (m, 2H), 0.00 (s, 9H).

Step 5: 5-(Difluoromethoxy)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

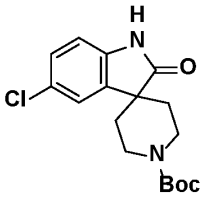


[0995] To a solution of tert-butyl 5-(difluoromethoxy)-2-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (139 mg, 0.28 mmol) in DCM (1.4 mL) was added TFA (530 µL, 5.6 mmol), then was stirred at room temperature for 2 h. The reaction mixture was then concentrated in vacuo and dissolved in MeOH (1.5 mL) and ammonium hydroxide (500 µL). After 5 min, the reaction mixture was concentrated and triturated with MTBE (5 mL). The solid was then filtered and dried in vacuo to afford 5-(difluoromethoxy)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-2**), which was used in the subsequent step without further purification. MS = 269.2 $[M+H]^+$.

General Procedure for Intermediates B-3 to B-5

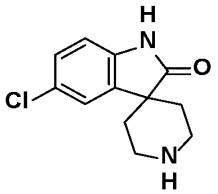


Step 1: *tert*-butyl 5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate



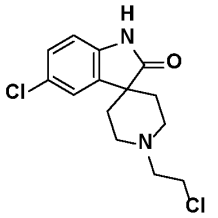
[0996] To a solution of *tert*-butyl 4-formylpiperidine-1-carboxylate (15.0 g, 70.3 mmol) and (4-chlorophenyl)hydrazine (15.1 g, 84.4 mmol, HCl salt) in $CHCl_3$ (200 mL) was added TFA (15.6 mL, 211 mmol). The mixture was stirred at 70 °C for 1 h, then cooled to 0 °C and *m*-CPBA (35.7 g, 85% purity, 176 mmol) was added. The mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was cooled to 0 °C then quenched with saturated aqueous Na_2CO_3 (300 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with saturated aqueous Na_2SO_3 (150 mL) and brine (3 x 100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 330 g cartridge, 0–100% EtOAc:petroleum ether) to give *tert*-butyl 5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (**Intermediate B-3**). MS = 281.1 $[M–C_4H_8+H]^+$.

Step 2: 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one



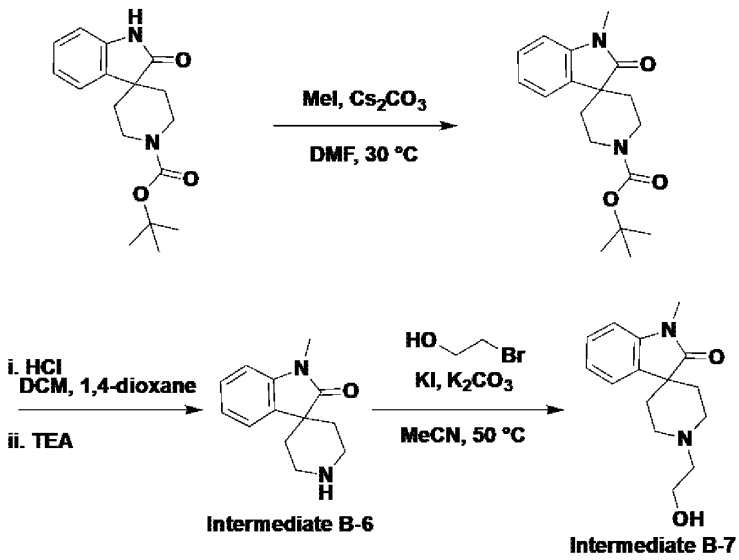
[0997] A solution of *tert*-butyl 5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (5.00 g, 14.9 mmol) and 4.0 M HCl in EtOAc (50 mL) was stirred for 1 h. The mixture was partially concentrated under reduced pressure to give a slurry. The suspension was filtered to isolate a solid, which was triturated with EtOAc (5 mL) and dried in vacuo to give 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, HCl salt). MS = 237.1 $[M+H]^+$.

Step 3: 5-chloro-1'-(2-chloroethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

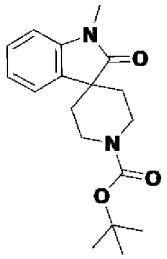


[0998] A 0 °C solution of 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (3.50 g, 12.8 mmol, HCl salt) and 2-chloroacetaldehyde in H_2O (2.68 mL, 40 wt%, 16.6 mmol) in DCM (50 mL) was stirred for 10 min, then $NaBH(OAc)_3$ (6.09 g, 28.7 mmol) was added. The mixture was stirred at 0 °C for 1 h and was then quenched with H_2O (30 mL). The resulting biphasic mixture was adjusted to pH = 9 with saturated aqueous Na_2CO_3 and was extracted with DCM (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give 5-chloro-1'-(2-chloroethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-5**). ^1H NMR (400 MHz, DMSO-d_6): δ 10.50 (s, 1H), 7.52 (br s, 1H), 7.25 (dd, J = 8.4, 2.0 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 3.75–3.72 (m, 2H), 2.90–2.56 (m, 6H), 1.79–1.70 (m, 4H). MS = 299.1 $[M+H]^+$.

General Procedure for Intermediates B-6 & B-7

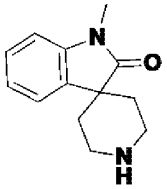


Step 1: *tert*-butyl 1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate



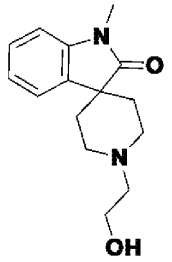
[0999] A mixture of tert-butyl 1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (10.0 g, 33.1 mmol), Cs_2CO_3 (21.6 g, 66.1 mmol), and MeI (20.6 mL, 331 mmol) in DMF (100 mL) was degassed and purged with N_2 (3x). The mixture was stirred at 30° C for 12 h under N_2 atmosphere and was then filtered and concentrated in vacuo to give tert-butyl 1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate, which was taken to the next step without further purification. MS = 317.1 $[M+H]^+$.

Step 2: 1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one



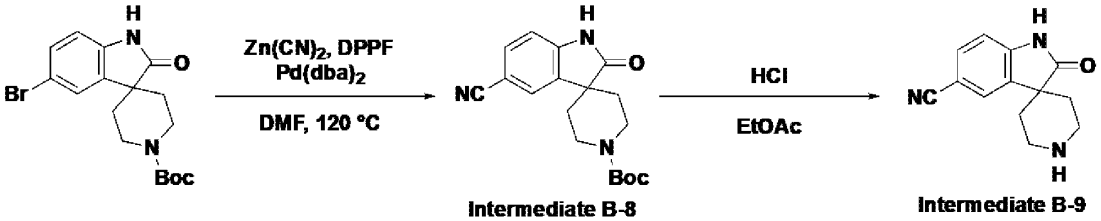
[1000] To a solution of *tert*-butyl 1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (33.1 mmol) in DCM (100 mL) was added 4.0 M HCl in 1,4-dioxane (40 mL, 160 mmol). The mixture was stirred for 12 h. The reaction mixture was adjusted to pH = 8 with the dropwise addition of TEA. The solution was filtered and concentrated in vacuo to give 1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one, which was taken to the next step without further purification (**Intermediate B-6**). MS = 217.1 $[M+H]^+$.

Step 3: 1'-(2-hydroxyethyl)-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

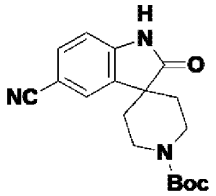


[1001] To a solution of 1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (33.1 mmol) and 2-bromoethanol (3.15 mL, 44.4 mmol) in MeCN (80 mL) was added KI (614 mg, 3.70 mmol) and K_2CO_3 (10.2 g, 74.0 mmol). The mixture was stirred at 50 °C for 12 h. After cooling to room temperature, the reaction mixture was filtered and concentrated in vacuo to give 1'-(2-hydroxyethyl)-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-7**), which was taken to the next steps without purification. MS = 261.2 $[M+H]^+$.

General Procedure for Intermediates B-8 & B-9

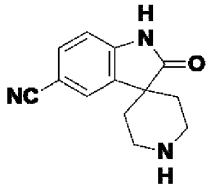


Step 1: *tert*-butyl 5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate



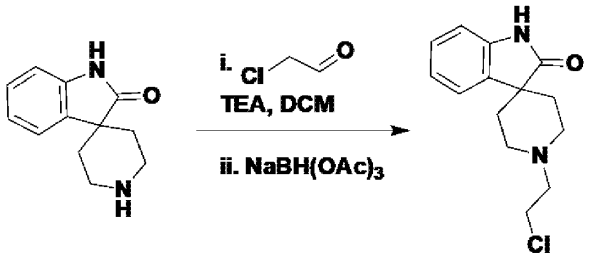
[1002] To a solution of tert-butyl 5-bromo-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (6.00 g, 15.7 mmol), $Zn(CN)_2$ (5.54 g, 47.2 mmol), DPPF (436 mg, 0.787 mmol) in DMF (120 mL) was added $Pd(dba)_2$ (905 mg, 1.57 mmol). The mixture was degassed and purged with N_2 (3x), and then the mixture was stirred at 120 °C for 12 h. After cooling to room temperature, the reaction mixture was quenched by the addition of H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 80 g cartridge, 0–50% EtOAc:petroleum ether) to give tert-butyl 5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (**Intermediate B-8**). MS = 272.2 $[M-C_4H_8+H]^+$.

Step 2: 2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile



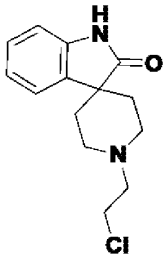
[1003] To a solution of tert-butyl 5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (3.80 g, 11.6 mmol) in EtOAc (40 mL) was added 4.0 M HCl in EtOAc (10 mL, 40 mmol). The mixture was stirred for 2 h, and the resulting solid was isolated via filtration to give 2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (**Intermediate B-9**, HCl salt), which was used in subsequent steps without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.19 (s, 1H), 9.33 (s, 2H), 7.70 (s, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 3.43–3.41 (m, 2H), 3.40–3.39 (m, 2H), 2.13–2.07 (m, 2H), 1.99–1.92 (m, 2H). MS = 228.3 $[M+H]^+$.

General Procedure for Intermediate B-10



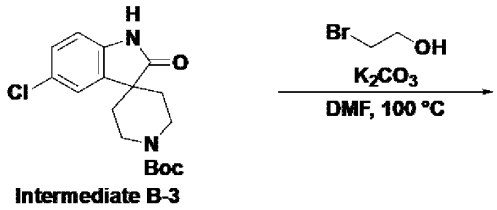
Intermediate B-10

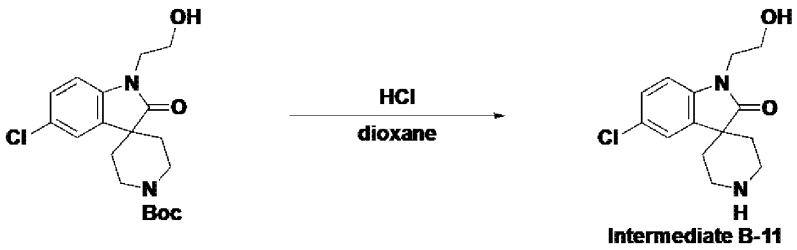
Step 1: 1'-(2-chloroethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one



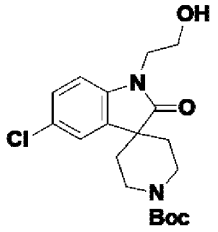
[1004] A mixture of 1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (1.00 g, 4.19 mmol, HCl salt), 2-chloroacetaldehyde in H_2O (1.35 mL, 40 wt%, 8.38 mmol) and TEA (1.75 mL, 12.8 mmol) in DCM (10 mL) was stirred for 2 h, and then $NaBH(OAc)_3$ (1.78 g, 8.38 mmol) was added. After stirring for 30 min, the reaction mixture was quenched by the addition of H_2O (10 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Isco 10 g cartridge, 0–100% EtOAc:petroleum ether) to give 1'-(2-chloroethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-10**). ^1H NMR (400 MHz, DMSO-d_6): δ 10.36 (s, 1H), 7.47–7.45 (m, 1H), 7.19 (app t, J = 7.6 Hz, 1H), 6.95 (app t, J = 7.6 Hz, 1H), 6.85–6.83 (m, 1H), 3.77–3.74 (m, 2H), 2.97–2.67 (m, 6H), 1.79–1.64 (m, 4H). MS = 265.1 $[M+H]^+$.

General Procedure for Intermediate B-11



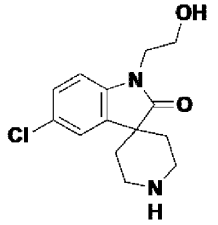


Step 1: *tert*-butyl 5-chloro-1-(2-hydroxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate



[1005] To a solution of tert-butyl 5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (**Intermediate B-3**, 500 mg, 1.48 mmol) and 2-bromoethanol (0.738 mL, 10.4 mmol) in DMF (5 mL) was added K_2CO_3 (1.03 g, 7.42 mmol). The mixture was stirred at 100 °C for 12 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–100% EtOAc:petroleum ether) to give tert-butyl 5-chloro-1-(2-hydroxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate. MS = 325.1 $[M–C_4H_8+H]^+$.

Step 2: 5-chloro-1-(2-hydroxyethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

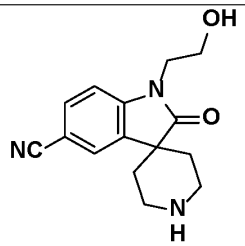
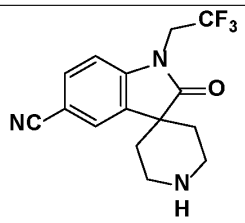
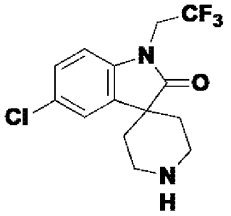
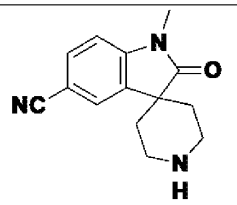


[1006] A solution of tert-butyl 5-chloro-1-(2-hydroxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (480 mg, 1.26 mmol) in 4.0 M HCl in 1,4-dioxane (2.0 mL, 8.0 mmol) was stirred at room temperature for 1 h. The mixture was concentrated in vacuo to give 5-chloro-1-(2-hydroxyethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-11**), which was used in the subsequent step without further purification. MS = 281.2 $[M+H]^+$.

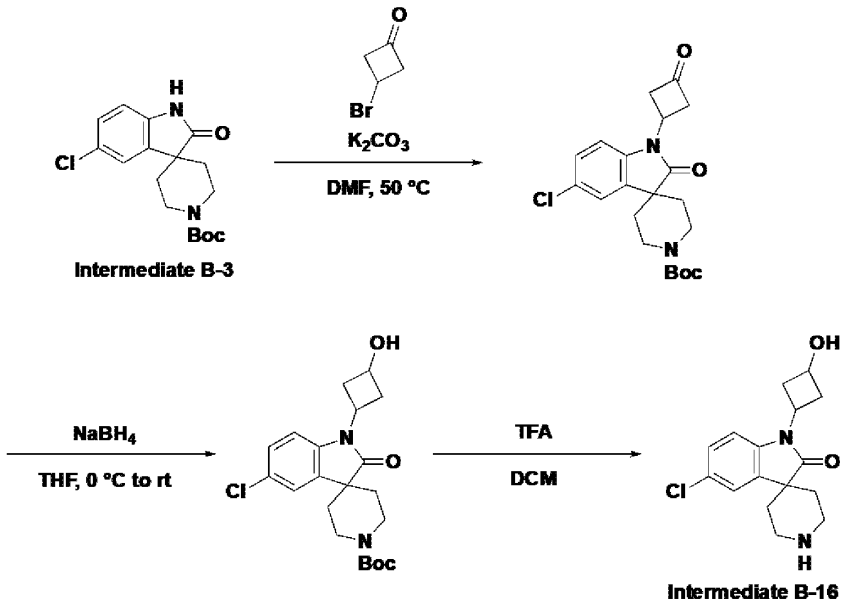
[1007] The following intermediates in Table 12 were prepared according to procedures similar those described for **Intermediate B-11** using the appropriate starting materials.

General Procedure for Intermediates B-12 to B-15

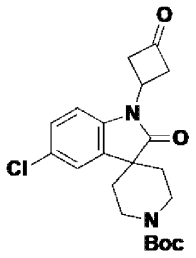
Table 12.

Intermediate #	Structure	Name	Exact Mass $[M+H]^+$
B-12		1-(2-hydroxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 272.1 Found 272.2
B-13		2-oxo-1-(2,2,2-trifluoroethyl)-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 310.1 Found 310.1
B-14		5-chloro-1-(2,2,2-trifluoroethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 319.1 Found 319.1
B-15		1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 242.1 Found 242.2

General Procedure for Intermediate B-16

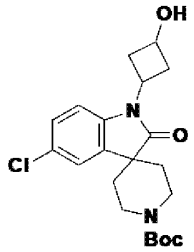


Step 1: *tert*-butyl 5-chloro-2-oxo-1-(3-oxocyclobutyl)-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate



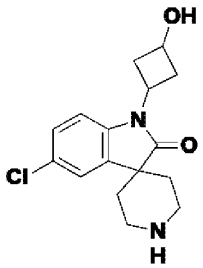
[1008] To a solution of *tert*-butyl 5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (**Intermediate B-3**, 1.00 g, 2.97 mmol) and 3-bromocyclobutanone (1.33 g, 8.91 mmol) in DMF (13 mL) was added K_2CO_3 (820 mg, 5.94 mmol). The mixture was stirred at 50 °C for 4 h. The reaction mixture was quenched with H_2O (30 mL), and then extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 40 g cartridge, 0–30% EtOAc:Petroleum ether) to give *tert*-butyl 5-chloro-2-oxo-1-(3-oxocyclobutyl)-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate. MS = 349.0 $[M–C_4H_8+H]^+$.

Step 2: *tert*-butyl 5-chloro-1-(3-hydroxycyclobutyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate



[1009] To a 0 °C solution of tert-butyl 5-chloro-2-oxo-1-(3-oxocyclobutyl)-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (500 mg, 1.23 mmol) in THF (10 mL) was added $NaBH_4$ (160 mg, 4.23 mmol). The mixture was allowed to warm to room temperature and stirred for 30 min. The reaction mixture was quenched with H_2O (20 mL) and then extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 20–30% EtOAc:petroleum ether) to give *tert*-butyl 5-chloro-1-(3-hydroxycyclobutyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate. ^{1}HNMR (400 MHz, DMSO-d_6): δ 7.60 (d, J = 2.0 Hz, 1H), 7.35–7.28 (m, 2H), 5.32 (d, J = 6.8 Hz, 1H), 4.22–4.14 (m, 1H), 3.99–3.91 (m, 1H), 3.72–3.63 (m, 4H), 2.66–2.52 (m, 4H), 1.77–1.62 (m, 4H), 1.44 (s, 9H).

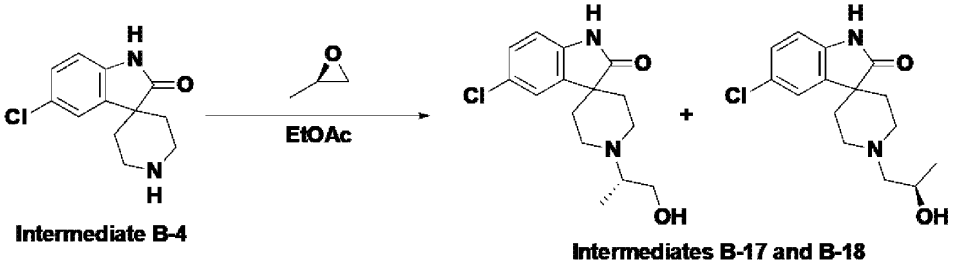
Step 3: 5-chloro-1-(3-hydroxycyclobutyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one



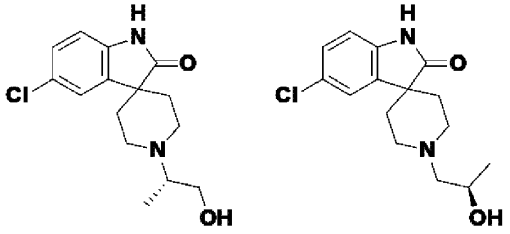
[1010] To a solution of tert-butyl 5-chloro-1-(3-hydroxycyclobutyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (400 mg, 0.983 mmol) in DCM (5 mL) was added TFA (1.50 g, 13.5 mmol). Then the mixture was stirred at room temperature for 1 h. The mixture was concentrated in vacuo, then diluted with H_2O (5 mL), and adjusted to pH = 7–8 via

dropwise addition of saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give 5-chloro-1-(3-hydroxycyclobutyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-16**), which was used in the subsequent step without further purification. MS =307.2 $[M+H]^+$.

General Procedure for Intermediates B-17 and B-18



Step 1: 5-chloro-1'-[(2*S*)-1-hydroxypropan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one and 5-chloro-1'-[(2*R*)-2-hydroxypropyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

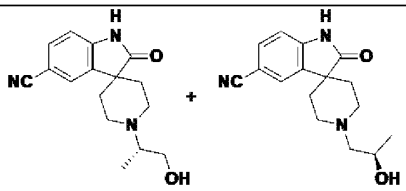
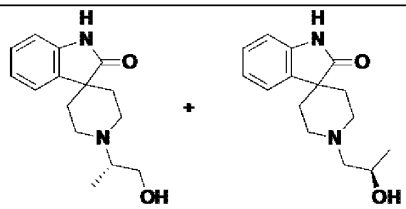


[1011] To a solution of 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 500 mg, 2.11 mmol) in EtOH (7 mL) was added (2R)-2-methyloxirane (0.592 mL, 8.45 mmol). The mixture was stirred at room temperature for 20 h. The reaction was concentrated in vacuo to give a mixture of 5-chloro-1'-[(2*S*)-1-hydroxypropan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one and 5-chloro-1'-[(2*R*)-2-hydroxypropyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediates B-17 and B-18**). MS = 295.2 $[M+H]^+$.

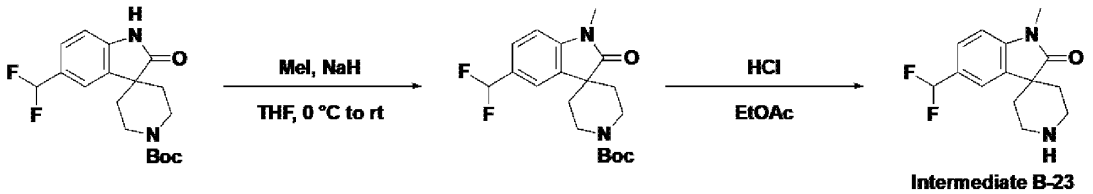
[1012] The following intermediates in Table 13 were prepared according to procedures similar those described for **Intermediates B-17** and **B-18** using the appropriate starting materials.

General Procedure for Intermediates B-19 to B-22

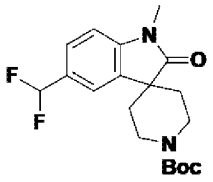
Table 13.

Inter-mediate #	Structure	Name	Exact Mass $[M+H]^+$	**Inter-mediate Starting Materials Used**
B-19 and **B-20**		(*S*)-1'-(1-hydroxypropan-2-yl)-2-oxospiro[indoline-3,4'-piperidine]-5-carbonitrile and 1'-[(2*R*)-2-hydroxypropyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 286.1 Found 286.2	**B-9**
B-21 and **B-22**		1'-[(2*S*)-1-hydroxypropan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one and 1'-[(2*R*)-2-hydroxypropyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 261.1 Found 261.3	n/a

General Procedure for Intermediate B-23

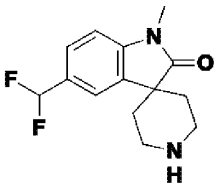


Step 1: *tert*-butyl 5-(difluoromethyl)-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate



[1013] To a 0 °C solution of tert-butyl 5-(difluoromethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (Procedure for Intermediate B-1, Step 3, 4.50 g, 12.8 mmol) in THF (50 mL) was added sodium hydride (613 mg, 60 wt% in mineral oil, 15.3 mmol). After stirring for 30 min, iodomethane (2.18 g, 15.32 mmol) was added to the mixture. The mixture was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give *tert*-butyl 5-(difluoromethyl)-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate, which was used in the subsequent step without further purification. MS = 311.1 $[M–C_4H_8+H]^+$.

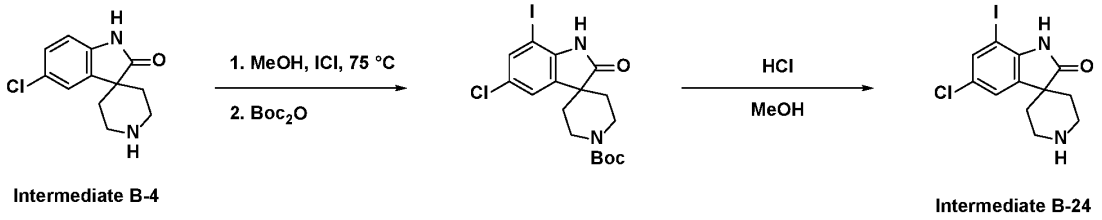
Step 2: 5-(difluoromethyl)-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one



[1014] To a 0 °C solution of *tert*-butyl 5-(difluoromethyl)-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (4.00 g, 10.9 mmol) in EtOAc (20 mL) was added 4.0 M HCl in EtOAc (20.0 mL, 80.0 mmol). The mixture was allowed to warm to room temperature and stirred for 2 h. The resulting solids were isolated by filtration and dried in vacuo to give 5-(difluoromethyl)-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-**

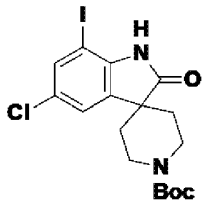
23, HCl salt), which was used in the subsequent steps without further purification. MS = 267.1 $[M+H]^+$.

General Procedure for Intermediate B-24



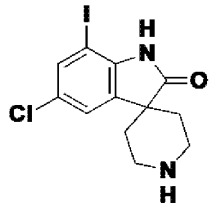
Intermediate B-4 Intermediate B-24

Step 1: *tert*-butyl 5-chloro-7-iodo-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate



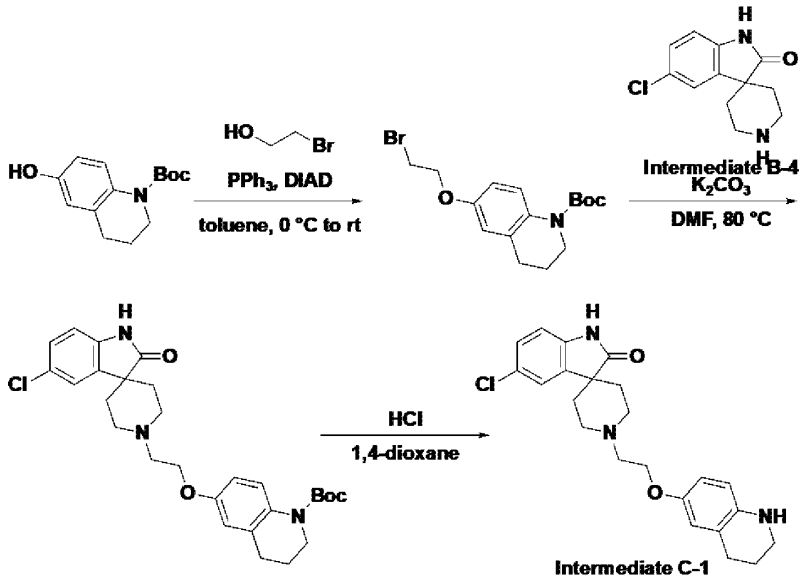
[1015] To a solution of 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 2.40 g, 10.1 mmol) in MeOH (20 mL) was added ICl (2.59 mL, 50.7 mmol). The mixture was stirred at 75 °C for 36 h. After cooling to room temperature, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (20 mL). The mixture was concentrated under reduced pressure to remove MeOH. The aqueous solution was adjusted to pH = 10 with saturated aqueous $NaHCO_3$, and then *tert*-butoxycarbonyl *tert*-butyl carbonate (2.21 g, 10.1 mmol) was added. The mixture was stirred at room temperature for 2 h. The reaction mixture was extracted with EtOAc **(3 x 20** mL). The combined organic layers were washed with brine (30 mL), dried over $\mathbf{Na_2SO_4}$, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 25 g cartridge, 0–10% MeOH:DCM) to give *tert*-butyl 5-chloro-7-iodo-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate.

Step 2: 5-chloro-7-iodo-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

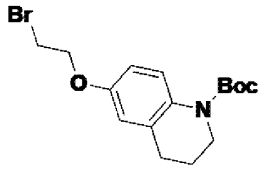


[1016] To a solution of *tert*-butyl 5-chloro-7-iodo-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (369 mg, 0.797 mmol) in MeOH (3 mL) was added 4.0 M HCl in MeOH (15 mL, 60 mmol). The mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo to give 5-chloro-7-iodo-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-24**). MS = 363.0 $[M+H]^+$.

General Procedure for Intermediate C-1



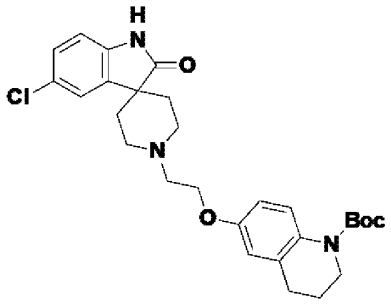
Step 1: ***tert*-butyl 6-(2-bromoethoxy)-1,2,3,4-tetrahydroquinoline-1-carboxylate**



[1017] To a vial holding *tert*-butyl 6-hydroxy-1,2,3,4-tetrahydroquinoline-1-carboxylate (0.500 g, 2.01 mmol) were added toluene (20 mL), bromoethanol (0.501 g, 4.01 mmol),

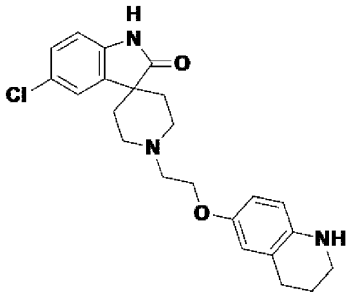
then polymer-bound PPh_3 (1.34 g, 3.00 mmol/g, 4.01 mmol). The reaction mixture was cooled to 0 °C and DIAD (0.608 g, 3.01 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 16 h. The solids were removed by filtration and washed with EtOAc (25 mL). The filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 25 g cartridge, 0–10% EtOAc:hexanes) to give *tert*-butyl 6-(2-bromoethoxy)-1,2,3,4-tetrahydroquinoline-1-carboxylate. MS = 300.0 $[M–C_4H_8+H]^+$.

Step 2: *tert*-butyl 6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-1,2,3,4-tetrahydroquinoline-1-carboxylate



[1018] A solution of *tert*-butyl 6-(2-bromoethoxy)-1,2,3,4-tetrahydroquinoline-1-carboxylate (200 mg, 0.561 mmol), 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 161 mg, 0.589 mmol, HCl salt) and K_2CO_3 (0.233 g, 1.68 mmol) in DMF (5.6 mL) was heated at 80 °C for 2 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (25 mL) and extracted with EtOAc (2 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 25 g cartridge, 0–15% MeOH:DCM) to give *tert*-butyl 6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-1,2,3,4-tetrahydroquinoline-1-carboxylate. MS = 512.2 $[M+H]^+$.

Step 3: 5-chloro-1'-[2-(1,2,3,4-tetrahydroquinolin-6-yloxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

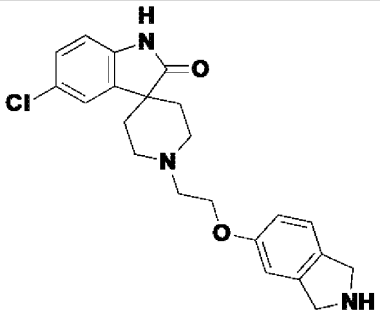


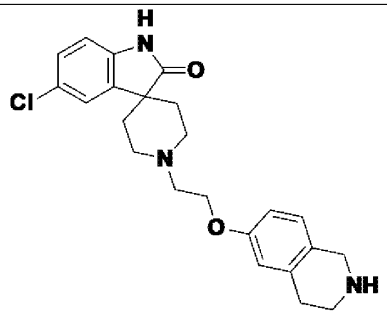
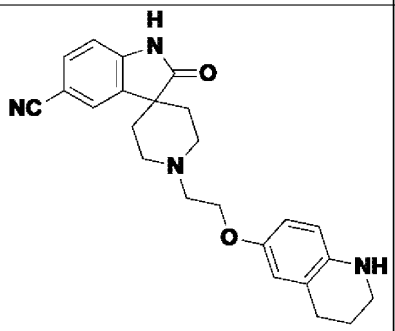
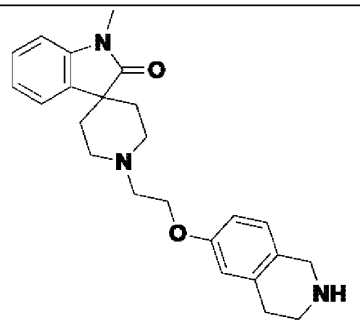
[1019] To a solution *tert*-butyl 6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-1,2,3,4-tetrahydroquinoline-1-carboxylate (177 mg, 0.346 mmol) in 1,4-dioxane (2 mL) was added 4.0 M HCl in 1,4-dioxane (2.16 mL, 8.64 mmol). The mixture was stirred for 1 h. The mixture was concentrated in vacuo to give 5-chloro-1'-[2-(1,2,3,4-tetrahydroquinolin-6-yloxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate C-1**, HCl salt), which was used in the subsequent step without further purification. MS = 412.1 $[M+H]^+$

[1020] The following intermediates in Table 14 were prepared according to procedures similar to steps 1–3 described for **Intermediate C-1** using the appropriate starting materials.

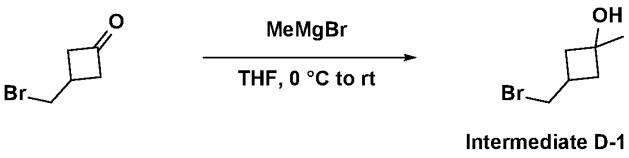
General Procedure for Intermediates C-2 to C-5

Table 14.

Inter-mediate #	Structure	Name	Exact Mass $[M+H]^+$	Intermediate Starting Materials Used
C-2		5-chloro-1'-[2-(2,3-dihydro-1H-isoindol-5-yloxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (HCl salt)	Calc'd 398.2 Found 398.1	**B-4**

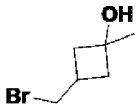
C-3		5-chloro-1'-[2-(1,2,3,4-tetrahydroisoquinolin-6-yloxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (HCl salt)	Calc'd 412.2 Found 412.2	**B-4**
C-4		2-oxo-1'-[2-(1,2,3,4-tetrahydroquinolin-6-yloxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (HCl salt)	Calc'd 403.2 Found 403.2	**B-9**
C-5		1-methyl-1'-[2-(1,2,3,4-tetrahydroisoquinolin-6-yloxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (HCl salt)	Calc'd 392.2 Found 392.1	**B-6**

General Procedure for Intermediate D-1



Intermediate D-1

Step 1: 3-(bromomethyl)-1-methylcyclobutan-1-ol



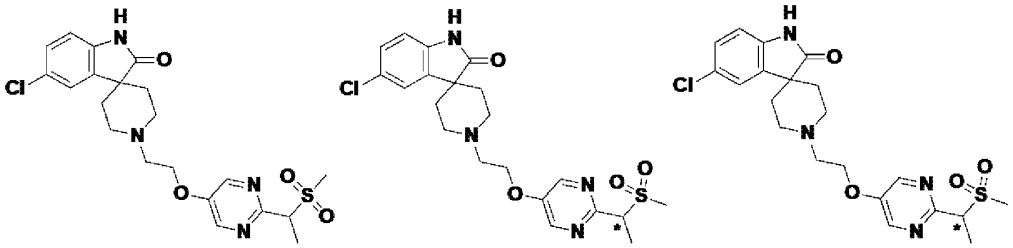
[1021] To a 0 °C solution of 3-(bromomethyl)cyclobutanone (3.00 g, 18.4 mmol) in THF (30 mL) was added 3.0 M MeMgBr in 2-MeTHF (6.8 mL, 20.4 mmol). The mixture was stirred at room temperature for 1 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl (30 mL), and then extracted with 3:1 DCM/MeOH (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give 3-(bromomethyl)-1-methylcyclobutan-1-ol (**Intermediate D-1**), which was used in the subsequent steps without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.13 (s, 1H), 3.52 (d, J = 7.6 Hz, 2H), 2.17 – 2.11 (m, 1H), 2.08 – 1.99 (m, 2H), 1.72 – 1.66 (m, 2H), 1.20 (s, 3H).

Example 1

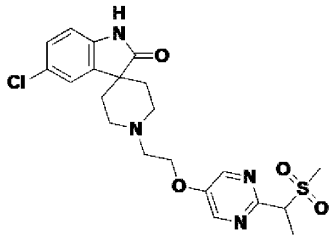
5-Chloro-1'-(2-{[2-(1-methanesulfonylethyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 1)

5-chloro-1'-[2-({2-[(1*S*) or (1*R*)-1-methanesulfonylethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 2) and

5-chloro-1'-[2-({2-[(1*R*) or (1*S*-1-methanesulfonylethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 3)

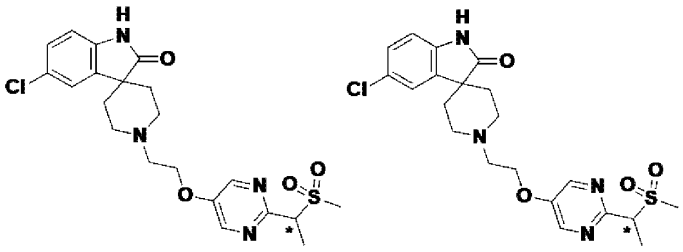


Step 1: 5-Chloro-1'-(2-{[2-(1-methanesulfonylethyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one



[1022] To a vial was added 5-(2-bromoethoxy)-2-(1-methanesulfonylethyl)pyrimidine (**Intermediate A-75**, 221 mg, 0.714 mmol), 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 150 mg, 0.55 mmol, HCl salt), followed by DMF (2.7 mL). K_2CO_3 (0.19 g, 1.37 mmol) was then added, and the reaction mixture was heated to 60 °C. After 2 h, the reaction was removed from heat and diluted with EtOAc, then filtered over Celite. The filtrate was concentrated, and the residue was diluted in a 1:1 mixture of MeCN and H_2O (3 mL). Purification by reverse phase preparative HPLC (Phenomenex Kinetex C_{18} column, 5–40% MeCN in water with 0.1% formic acid modifier) afforded 5-chloro-1'-(2-{[2-(1-methanesulfonylethyl)pyrimidin-5-yl]oxy}ethyl)-1H-spiro[indole-3,4'-piperidin]-2-one (**Compound 1**). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.42 (s, 1H), 8.58 (s, 2H), 7.44 (d, J = 2.1 Hz, 1H), 7.17 (dd, J = 8.3, 2.1 Hz, 1H), 6.78 (d, J = 8.3 Hz, 1H), 4.58 (q, J = 7.2 Hz, 1H), 4.29–4.27 (m, 2H), 2.94 (s, 3H), 2.91–2.79 (m, 4H), 2.66–2.64 (m, 2H), 1.71–1.69 (m, 2H), 1.66–1.61 (m, 5H). MS = 465.03 $[M+H]^+$.

Step 2: 5-chloro-1'-[2-({2-[(1*S*) or (1*R*)-1-methanesulfonylethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 2) and 5-chloro-1'-[2-({2-[(1*R*) or (1*S*)-1-methanesulfonylethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 3)

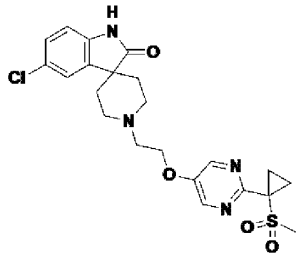


[1023] 5-Chloro-1'-(2-{[2-(1-methanesulfonylethyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one was separated by preparative chiral SFC (Daicel Chiralpak AD-3, 55% isopropanol with 0.1% NH_4OH in CO_2). The first eluting enantiomer of the title

compound, 5-chloro-1'-[2-({2-[(1*S*) or (1*R*)-1-methanesulfonylethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 2**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.45 (s, 1H), 8.61 (s, 2H), 7.47 (d, J = 1.6 Hz, 1H), 7.20 (dd, J = 8.4, 2.0 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 4.62 (q, J = 7.2 Hz, 1H), 4.31 (t, J = 5.6 Hz, 2H), 2.98 (s, 3H), 2.93–2.82 (m, 4H), 2.71–2.62 (m, 2H), 1.78–1.71 (m, 2H), 1.70–1.63 (m, 5H). MS = 465.1 $[M+H]^+$. The second eluting enantiomer of the title compound, 5-chloro-1'-[2-({2-[(1*R*) or (1*S*)-1-methanesulfonylethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 3**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.50 (s, 1H), 8.66 (s, 2H), 7.52 (s, 1H), 7.29–7.22 (m, 1H), 6.86 (d, J = 8.3 Hz, 1H), 4.67 (q, J = 7.0 Hz, 1H), 4.36 (br s, 2H), 3.03 (s, 3H), 2.98–2.87 (m, 4H), 2.76–2.67 (m, 2H), 1.79–1.78 (m, 2H) 1.72–1.70 (m, 5H). MS = 465.1 $[M+H]^+$.

Example 2

5-chloro-1'-(2-{[2-(1-methanesulfonylcyclopropyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 4)

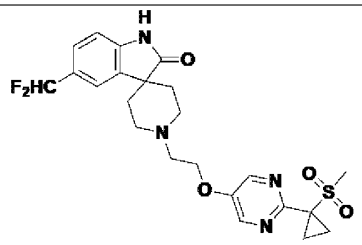


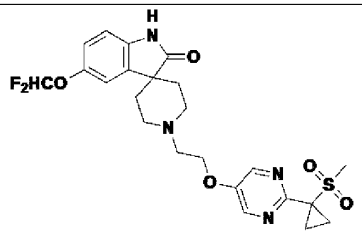
[1024] To a solution of 5-(2-bromoethoxy)-2-(1-methanesulfonylcyclopropyl)pyrimidine (**Intermediate A-76**, 300 mg, 0.93 mmol) and 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 0.306 g, 1.12 mmol, HCl salt) in DMF (4.7 mL) was added K_2CO_3 (0.387 g, 2.80 mmol). The reaction mixture was heated to 60 °C for 2 h. The reaction was allowed to cool to room temperature, diluted in H_2O (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by reverse phase preparative HPLC (Phenomenex Kinetex C_{18} column, 5–40% MeCN in water with 0.1% formic acid modifier) gave 5-chloro-1'-(2-{[2-(1-methanesulfonylcyclopropyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 4**). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.49 (s, 1H), 8.61 (s, 2H), 7.50 (d, J = 2.1 Hz, 1H), 7.23 (dd, J = 8.2, 2.1 Hz, 1H),

6.84 (d, J = 8.3 Hz, 1H), 4.34 (t, J = 5.6 Hz, 2H), 3.36 (s, 3H), 2.96–2.85 (m, 4H), 2.73–2.68 (m, 2H), 1.80–1.67 (m, 6H), 1.60–1.58 (m, 2H). MS = 477.12 $[M+H]^+$.

[1025] The following compounds in Table 15 were prepared according to procedures analogous to those described for **Compound 4** using the appropriate starting materials.

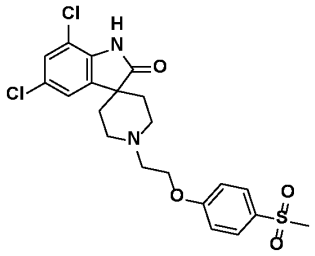
Table 15.

#	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Inter-mediates Used	HNMR Spectra
5		5-(difluoromethyl)-1'-(2-{[2-(1-methanesulfonylcyclopropyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 493.2 Found 493.2	**A-76** and **B-1**	^{1}H NMR (500 MHz, $CDCl_3$, 25/26 H): δ 8.34 (s, 2H), 7.69 (s, 1H), 7.39 (s, 1H), 7.34–7.25 (m, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.54 (t, J = 56.5 Hz, 1H), 4.35 (t, J = 5.1 Hz, 2H), 3.30 (t, J = 11.8 Hz, 2H), 3.26 (s, 3H), 3.14 (t, J = 5.1 Hz, 2H), 3.06 (d, J = 11.4 Hz, 1H), 2.22 (s, 2H), 1.94–1.82 (m, 4H), 1.72–1.57 (m, 2H).

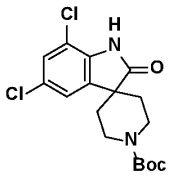
6		5-(difluoromethoxy)-1'-(2-{[2-(1-methanesulfonylcyclopropyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 509.2 Found 509.1	**A-76** and **B-2**	^{1}H NMR (500 MHz, DMSO-d_6): δ 10.39 (s, 1H), 8.55 (s, 2H), 8.07 (s, 1H), 7.03 (t, J = 74.7 Hz, 1H), 6.95 (d, J = 8.4, 1H), 6.79 (d, J = 8.4 Hz, 1H), 4.30 (t, J = 5.5 Hz, 2H), 3.29 (br s, 3H), 2.99–2.86 (m, 4H), 2.75–2.66 (m, 2H), 1.77–1.73 (m, 2H), 1.68–1.65 (m, 4H), 1.54–1.51 (m, 2H).

Example 3

5,7-dichloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 7)

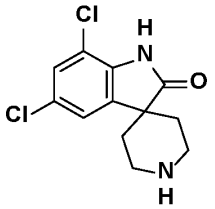


Step 1: *tert*-butyl 5,7-dichloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate



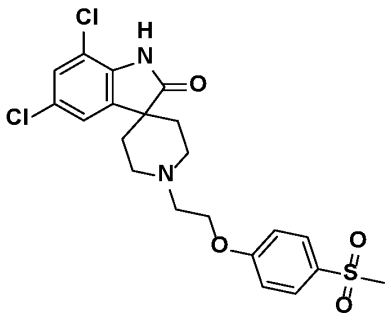
[1026] To a solution of (2,4-dichlorophenyl)hydrazine (2.60 g, 12.2 mmol, HCl salt) in $CHCl_3$ (30 mL) was added TEA (1.30 mL, 9.36 mmol), *tert*-butyl 4-formylpiperidine-1-carboxylate (2.00 g, 9.36 mmol) and TFA (2.80 mL, 28.1 mmol). The mixture was stirred at 70 °C for 17 h. The mixture was cooled to 0 °C and *m*-CPBA (1.14 g, 85% purity, 5.63 mmol) was added in portions. Then the mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with saturated aqueous Na_2CO_3 (60 mL) and extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$ (50 mL) and brine (2 x 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 25 g cartridge, 0–40% EtOAc:petroleum ether). The residue was further purified by reverse phase preparative HPLC (Phenomenex Luna C_{18} column, 40–75% MeCN: 10 mM TFA in H_2O) to give *tert*-butyl 5,7-dichloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate. MS = 315.0 $[M–C_4H_8+H]^+$.

Step 2: 5,7-dichloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one



[1027] To a solution of *tert*-butyl 5,7-dichloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (280 mg, 0.75 mmol) in EtOAc (5 mL) was added 4.0 M HCl in EtOAc (10 mL, 40 mmol). The mixture was stirred at room temperature for 1 h. The mixture was concentrated under reduced pressure to give 5,7-dichloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one. MS = 271.0 / 273.0 $[M+H]^+$.

Step 3: 5,7-dichloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 7)

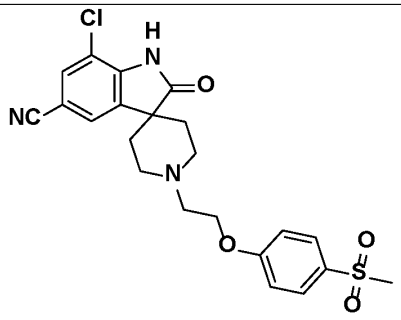
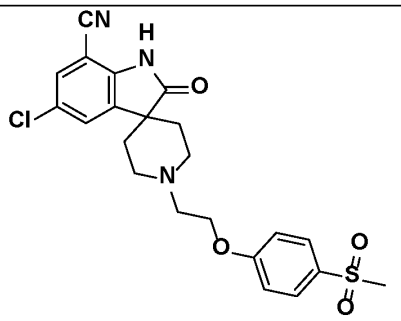


[1028] A mixture of 5,7-dichloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (100 mg, 0.325 mmol, HCl salt), 1-(2-bromoethoxy)-4-methylsulfonyl-benzene (**Intermediate A-3**, 77.1 mg, 0.276 mmol) and K_2CO_3 (89.9 mg, 650 mmol) in MeCN (4 mL) was stirred at 70 °C for 3 h. After cooling to the reaction to room temperature, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters Xbridge BEH C_{18} column, 30–60% MeCN:10 mM NH_4HCO_3 in H_2O) to give 5,7-dichloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 7**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.90 (br s, 1H), 7.85–7.83 (d, J = 8.8 Hz, 2H), 7.53 (s, 1H), 7.43–7.42 (m, 1H), 7.19 (d, J = 8.8 Hz, 2H), 4.25 (t, J = 5.6 Hz, 2H), 3.16 (s, 3H), 2.92–2.86 (m, 4H), 2.70–2.74 (m, 2H), 1.80–1.78 (m, 4H). MS = 469.1 $[M+H]^+$.

[1029] The following compounds in Table 16 were prepared according to procedures similar to steps 1–3 described for **Compound 7** using the appropriate starting materials.

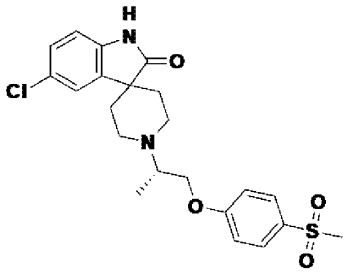
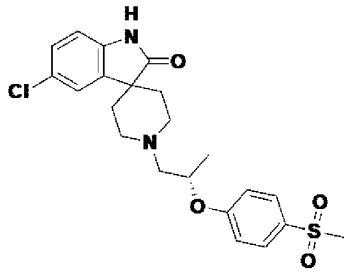
Table 16.

#	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Inter-mediate Used

8		7-chloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 460.1 Found 460.1	**A-3**
9		5-chloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-7-carbonitrile	Calc'd 460.1 Found 460.2	**A-3**

Example 4

5-chloro-1'-[(2*S*)-1-(4-methanesulfonylphenoxy)propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 10) and 5-chloro-1'-[(2*S*)-2-(4-methanesulfonylphenoxy)propyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 11)

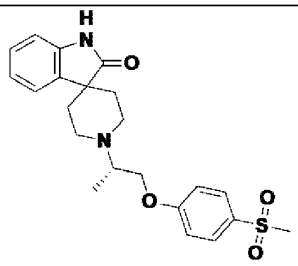



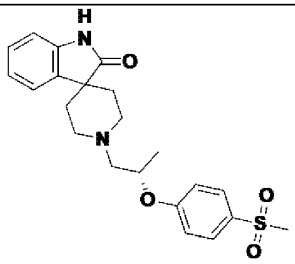
[1030] To a mixture of 5-chloro-1'-[(2*S*)-1-hydroxypropan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one and 5-chloro-1'-[(2*R*)-2-hydroxypropyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediates B-17** and **B-18**, 200 mg, 0.678 mmol) and 4-methylsulfonylphenol (175 mg, 1.02 mmol) in THF (1 mL) was added PPh_3 (267 mg, 1.02 mmol). The mixture was cooled to 0 °C, and DIAD (0.198 mL, 1.02 mmol) was added dropwise. The mixture was stirred at 25 °C for 3 h.

The reaction mixture was cooled to 0 °C and quenched with H_2O (10 mL), then extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (8 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–100% EtOAc:petroleum ether). The residue was further purified by reverse phase preparative HPLC (Waters Xbridge BEH C_{18} column, 30–50% MeCN:10 mM NH_4HCO_3 in H_2O). The first eluting product, 5-chloro-1'-[(2*S*)-1-(4-methanesulfonylphenoxy)propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 10**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 1H), 7.85 (d, J = 8.8 Hz, 2H), 7.44 (s, 1H), 7.24–7.21 (m, 3H), 6.84 (d, J = 8.0 Hz, 1H), 4.26–4.22 (m, 1H), 4.10–4.06 (m, 1H), 3.16 (s, 3H), 3.14–3.12 (m, 1H), 3.02–3.00 (m, 2H), 2.84–2.74 (m, 2H), 1.77–1.66 (m, 4H), 1.16 (d, J = 6.4 Hz, 3H), MS = 449.1 $[M+H]^+$. The second eluting product, 5-chloro-1'-[(2*S*)-2-(4-methanesulfonylphenoxy)propyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 11**): ^{1}H NMR (400 MHz , DMSO-d_6): δ 10.49 (s, 1H), 7.83 (d, J = 8.8 Hz, 2H), 7.47 (s, 1H), 7.24–7.19 (m, 3H), 6.83 (d, J = 8.4 Hz, 1H), 4.89–4.85 (m, 1H), 3.16 (s, 3H), 2.90–2.88 (m, 2H), 2.78–2.76 (m, 1H), 2.70–2.63 (m, 3H), 1.75–1.64 (m, 4H), 1.30 (d, J = 6.0 Hz, 3H). MS = 449.1 $[M+H]^+$.

[1031] The following compounds in Table 17 were prepared according to procedures similar to steps described for **Compound 10** and **Compound 11** using the appropriate starting materials.

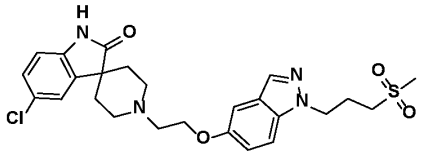
Table 17.

#	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Step 2 Column	Step 2 Elution Order	Inter-mediates Used
12		1'-[(2*S*)-1-(4-methanesulfonylphenoxy)propan-2-yl]-1,2-dihydrospiro[indole-3,4'-	Calc'd 415.1 Found 415.2	Waters Xbridge BEH C_{18} column	1st	**B-21 & B-22**

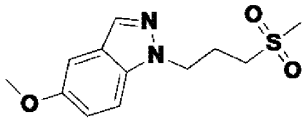
		piperidin]-2-one				
13		1'-[(2*S*)-2-(4-methanesulfonylphenoxy)propyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 415.1 Found 415.1	Waters Xbridge BEH C_{18} column	2nd	**B-21 & B-22**

Example 5

5-chloro-1'-(2-{[1-(3-methanesulfonylpropyl)-1H-indazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 14)



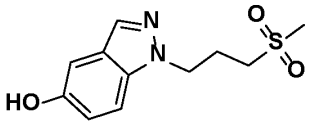
Step 1: 1-(3-methanesulfonylpropyl)-5-methoxy-1H-indazole



[1032] A mixture of 5-methoxy-1H-indazole (200 mg, 1.35 mmol), 3-methylsulfonylpropyl methanesulfonate (292 mg, 1.35 mmol) and Cs_2CO_3 (880 mg, 2.70 mmol) in DMF (5 mL) was stirred at 80 °C for 2 h. The reaction mixture was cooled to 0 °C and quenched by the addition of H_2O (20 mL), then extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by preparative TLC (SiO_2, 100% EtOAc). The lower polarity (higher R_f) product, desired 1-(3-methanesulfonylpropyl)-5-methoxy-1H-indazole: ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 (d, J = 0.8 Hz, 1H), 7.59 (d, J = 9.2 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 7.06 (dd, J = 9.2, 2.4 Hz,

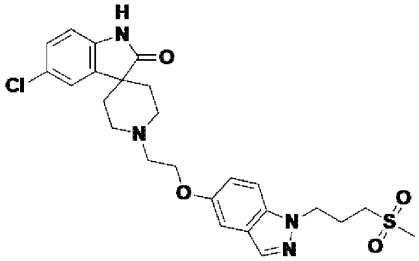
1H), 4.50 (t, J = 7.2 Hz, 2H), 3.78 (s, 3H), 3.08 (dd, J = 10.4, 5.6 Hz, 2H), 2.96 (s, 3H), 2.26-2.18 (m, 2H). MS = 269.1 $[M+H]^+$. The higher polarity product, byproduct 2-(3-methanesulfonylpropyl)-5-methoxy-2H-indazole: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21 (s, 1H), 7.51 (d, J = 9.2 Hz, 1H), 7.00 (d, J = 2.4 Hz, 1H), 6.90 (dd, J = 9.2, 2.8 Hz, 1H), 4.50 (t, J = 6.8 Hz, 2H), 3.75 (s, 3H), 3.11–3.07 (m, 2H), 2.98 (s, 3H), 2.36–2.28 (m, 2H). MS = 269.1 $[M+H]^+$.

Step 2: 1-(3-methanesulfonylpropyl)-1H-indazol-5-ol



[1033] To a 0 °C solution of 1-(3-methanesulfonylpropyl)-5-methoxy-1H-indazole (150 mg, 0.559 mmol) in DCM (8 mL) was added BBr_3 (215 µL, 2.24 mmol) dropwise. The mixture was stirred at room temperature for 10 h. The reaction mixture was cooled to 0 °C and quenched by the addition of H_2O (10 mL), then adjusted to pH = 9 with saturated aqueous $NaHCO_3$ and extracted with DCM (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo give 1-(3-methanesulfonylpropyl)-1H-indazol-5-ol. MS = 255.1 $[M+H]^+$.

Step 3: 5-chloro-1'-(2-{[1-(3-methanesulfonylpropyl)-1H-indazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 14)

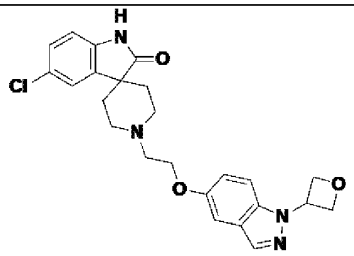
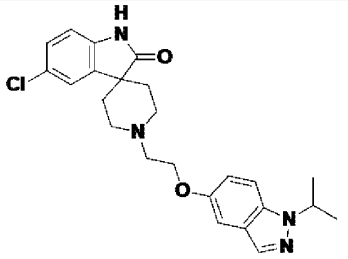


[1034] A mixture of 1-(3-methanesulfonylpropyl)-1H-indazol-5-ol (30 mg, 0.118 mmol), 5-chloro-1'-(2-chloroethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-5**, 52.9 mg, 0.177 mmol), NaI (0.8 mg, 5.90 $u$mol) and K_2CO_3 (16.3 mg, 0.118 mmol) in acetone (1 mL) was stirred at 50 °C for 16 h. After cooling to the reaction to room temperature, the mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters Xbridge BEH C_{18} column, 25–60% MeCN:10 mM NH_4HCO_3 in H_2O) to

give 5-chloro-1'-(2-{[1-(3-methanesulfonylpropyl)-1H-indazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 14**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.50 (s, 1H), 7.96 (s, 1H), 7.60 (d, J = 9.2 Hz, 1H), 7.51 (d, J = 2.0 Hz, 1H), 7.24–7.22 (m, 2H), 7.10 (d, J = 8.8 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 4.50 (t, J = 6.8 Hz, 2H), 4.16 (t, J = 6.4 Hz, 2H), 3.08 (t, J = 8.0 Hz, 2H), 2.96 (s, 3H), 2.94–2.87 (m, 4H), 2.72–2.70 (m, 2H), 2.22–2.20 (m, 2H), 1.79–1.70 (m, 4H). MS = 517.2 $[M+H]^+$.

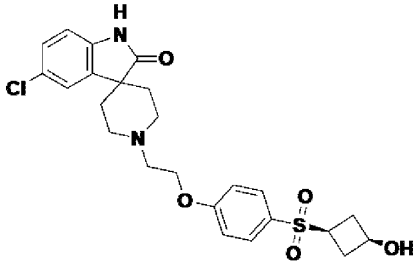
[1035] The following compounds in Table 18 were prepared according to procedures similar to steps 1–3 described for **Compound 14** using the appropriate starting materials. Step 1 separation of indazole regiosomers was performed using normal phase SiO_2 column chromatography.

Table 18.

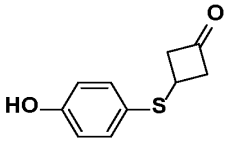
#	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Step 1 Elution Order	Inter-mediate Used
15		5-chloro-1'-(2-{[1-(oxetan-3-yl)-1H-indazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 453.1 Found 453.2	First; lower polarity product	**B-5**
16		5-chloro-1'-(2-{[1-(propan-2-yl)-1H-indazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 439.1 Found 439.3	First; lower polarity product	**B-5**

Example 6

5-chloro-1'-[2-(4-{[(cis)-3-hydroxycyclobutyl]sulfonyl}phenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 17)

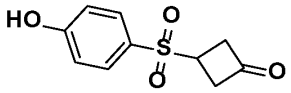


Step 1: 3-[(4-hydroxyphenyl)sulfanyl]cyclobutan-1-one



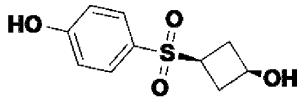
[1036] To a solution of 4-sulfanylphenol (200 mg, 1.59 mmol) and 3-bromocyclobutanone (236 mg, 1.59 mmol) in acetone (2 mL) was added K_2CO_3 (219 mg, 1.59 mmol) and NaI (237 mg, 1.59 mmol). The mixture was stirred at 50 °C for 3 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by preparative TLC (SiO_2, 1:2 EtOAc:petroleum ether) to give 3-[(4-hydroxyphenyl)sulfanyl]cyclobutan-1-one. MS = 195.0 $[M+H]^+$.

Step 2: 3-(4-hydroxybenzenesulfonyl)cyclobutan-1-one



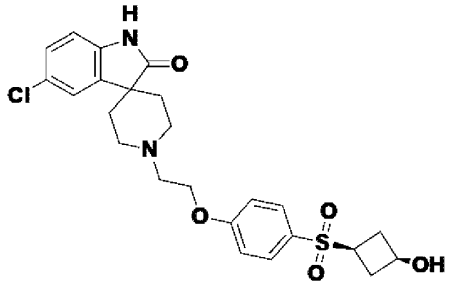
[1037] To a 0 °C solution of 3-[(4-hydroxyphenyl)sulfanyl]cyclobutan-1-one (50.0 mg, 0.257 mmol) in THF (2 mL) and H_2O (1 mL) was added Oxone (316 mg, 0.514 mmol). The mixture was stirred at room temperature for 1 h. The reaction mixture was cooled to 0 °C and quenched by the addition of saturated aqueous $Na_2S_2O_3$ (3 mL), then diluted with H_2O (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by preparative TLC (SiO_2, 1:1 EtOAc:petroleum ether) to give 3-(4-hydroxybenzenesulfonyl)cyclobutan-1-one. MS = 225.0 $[M–H]^+$.

Step 3: Preparation of 4-{[(*cis*)-3-hydroxycyclobutyl]sulfonyl}phenol



[1038] To a 0 °C solution of 3-[(4-hydroxyphenyl)sulfanyl]cyclobutan-1-one (75.0 mg, 0.331 mmol) in THF (5 mL) was added $NaBH_4$ (25 mg, 0.662 mmol). The mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL), diluted with H_2O (5 mL), and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give crude 4-{[(*cis*)-3-hydroxycyclobutyl]sulfonyl}phenol, which was carried onto the next step without additional purification. MS = 229.1 $[M+H]^+$.

Step 4: 5-chloro-1'-[2-(4-{[(*cis*)-3-hydroxycyclobutyl]sulfonyl}phenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 17)

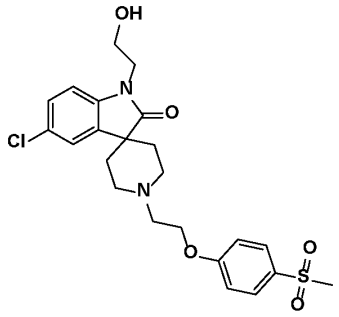


[1039] To a solution of 4-{[(*cis*)-3-hydroxycyclobutyl]sulfonyl}phenol (100 mg, 0.438 mmol) and 5-chloro-1'-(2-chloroethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-5**, 196 mg, 0.657 mmol) in DMF (3 mL) was added Ag_2O (203 mg, 0.876 mmol). The mixture was stirred at 50 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by reverse phase preparative HPLC (Waters Xbridge BEH C_{18} column, 25–55% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-[2-(4-{[(*cis*)-3-hydroxycyclobutyl]sulfonyl}phenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 17**). ^1H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 1H), 7.73 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 1.6 Hz, 1H), 7.24–7.21 (m, 1H), 7.19 (d, J = 9.2 Hz, 2H), 6.84 (d, J = 8.4 Hz, 1H), 5.44 (d, J = 6.4 Hz, 1H), 4.24 (t, J = 6.4 Hz, 2H), 3.99–3.91 (m,

1H), 3.53–3.45 (m, 1H), 2.95–2.86 (m, 4H), 2.71–2.66 (m, 2H), 2.32–2.26 (m, 2H), 2.15–2.03 (m, 2H), 1.80–1.68 (m, 4H). MS = 491.1 $[M+H]^+$.

Example 7

5-chloro-1-(2-hydroxyethyl)-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 18)

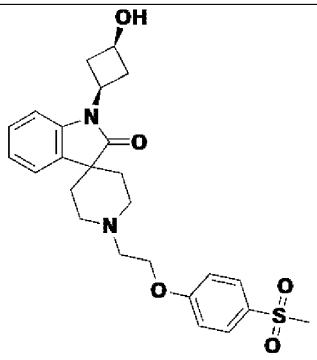
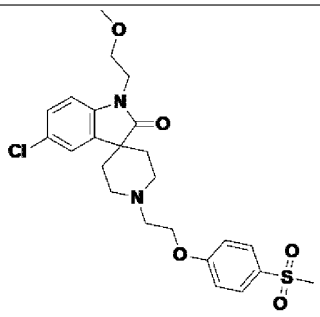
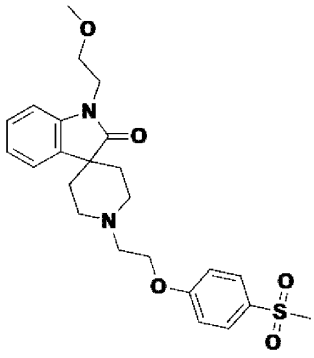


[1040] To a solution of 5-chloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 69**, 100 mg, 0.230 mmol) in DMF (1.0 mL) was added K_2CO_3 (159 mg, 1.15 mmol) and 2-bromoethanol (54.6 μL, 0.768 mmol). The mixture was stirred at 80 °C for 12 h. After cooling to room temperature, the mixture was filtered and concentrated in vacuo. The residue was purified by reverse phase preparative HPLC (Waters Xbridge BEH C_{18} column, 20–50% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1-(2-hydroxyethyl)-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 18**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.84 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 2.4 Hz, 1H), 7.32 (dd, J = 8.4, 2.0 Hz, 1H), 7.20 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 8.4 Hz, 1H), 4.82 (t, J = 6.0 Hz, 1H), 4.26 (t, J = 6.0 Hz, 2H), 3.73–3.68 (m, 2H), 3.57–3.54 (m, 2H), 3.16 (s, 3H), 2.98–2.86 (m, 4H), 2.76–2.69 (m, 2H), 1.77 (t, J = 5.2 Hz, 4H). MS = 479.1 $[M+H]^+$.

[1041] The following compounds in Table 19 were prepared according to procedures similar to steps described for **Compound 18** using the appropriate starting materials.

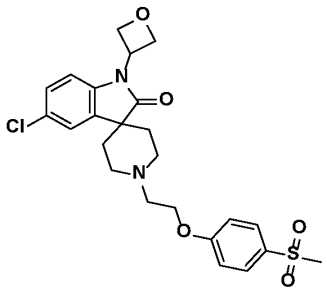
Table 19.

#	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Inter-mediated Used

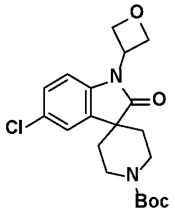
19		1'-[2-(4-methanesulfonylphenoxy)ethyl]-1-[(*cis*)-3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 471.1 Found 471.2	**Compound 73**
20		5-chloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1-(2-methoxyethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 493.2 Found 493.2	**Compound 69**
21		1'-[2-(4-methanesulfonylphenoxy)ethyl]-1-(2-methoxyethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 459.2 Found 459.2	**Compound 73**

Example 8

5-chloro-1'-(2-(4-(methylsulfonyl)phenoxy)ethyl)-1-(oxetan-3-yl)spiro[indoline-3,4'-piperidin]-2-one (Compound 22)

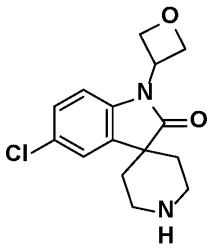


Step 1: *tert*-butyl 5-chloro-1-(oxetan-3-yl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate



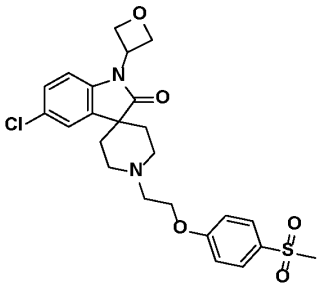
[1042] To a solution of *tert*-butyl 5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (**Intermediate B-3**, 300 mg, 0.891 mmol) in DMF (5 mL) were added K_2CO_3 (369 mg, 2.67 mmol) and 3-iodooxetane (655 mg, 3.56 mmol). The mixture was stirred at 100 °C for 12 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–18% EtOAc:petroleum ether) to give *tert*-butyl 5-chloro-1-(oxetan-3-yl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate. MS = 393.2 $[M+H]^+$.

Step 2: 5-chloro-1-(oxetan-3-yl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one



[1043] A solution of *tert*-butyl 5-chloro-1-(oxetan-3-yl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (200 mg, 509 mmol) in DCM (4 mL) and TFA (0.5 mL) was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to give 5-chloro-1-(oxetan-3-yl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one. MS = 293.1 $[M+H]^+$.

Step 3: 5-chloro-1'-(2-(4-(methylsulfonyl)phenoxy)ethyl)-1-(oxetan-3-yl)spiro[indoline-3,4'-piperidin]-2-one (Compound 22)

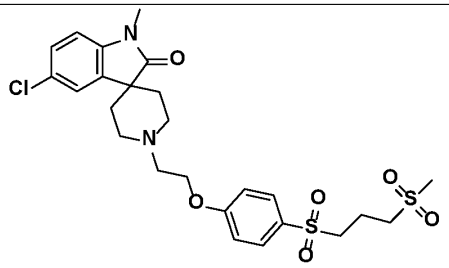
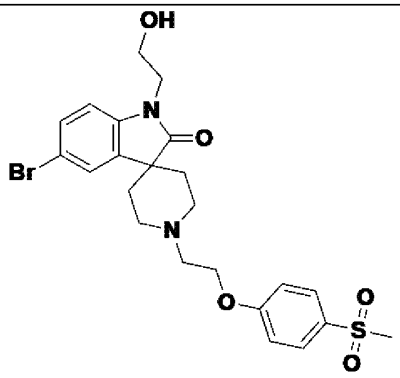
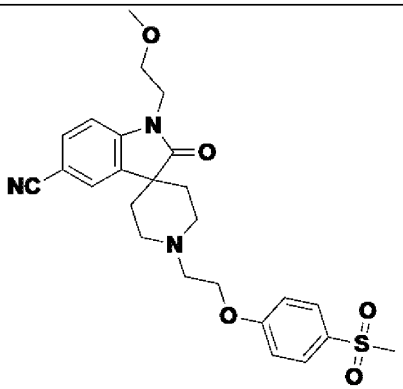


[1044] To a solution of 5-chloro-1-(oxetan-3-yl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (150 mg, 0.369 mmol, TFA salt) in MeCN (3 mL) were added K_2CO_3 (102 mg, 0.737 mmol) and 1-(2-bromoethoxy)-4-methanesulfonylbenzene (**Intermediate A-3**, 154 mg, 0.553 mmol). The mixture was stirred at 80 °C for 12 h. After cooling to room temperature, the reaction mixture was filtered and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters Xbridge BEH C_{18} column, 30–55% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-(2-(4-(methylsulfonyl)phenoxy)ethyl)-1-(oxetan-3-yl)spiro[indoline-3,4'-piperidin]-2-one (**Compound 22**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.84 (d, J = 8.8 Hz, 2H), 7.61 (s, 1H), 7.42–7.34 (m, 2H), 7.19 (d, J = 8.8 Hz, 2H), 5.43–5.35 (m, 1H), 5.00–4.87 (m, 4H), 4.25 (t, J = 5.6 Hz, 2H), 3.16 (s, 3H), 2.94–2.88 (m, 4H), 2.75–2.19 (m, 2H), 1.85–1.75 (m, 4H). MS = 491.1 $[M+H]^+$.

[1045] The following compounds in Table 20 were prepared according to procedures similar to steps 1–3 described for **Compound 22** using the appropriate starting materials.

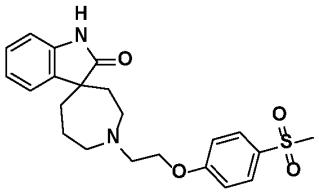
Table 20.

#	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Intermediate Used

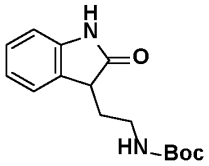
23		5-chloro-1'-{2-[4-(3-methanesulfonylpropanesulfonyl)phenoxy]ethyl}-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 555.1 Found 555.2	**A-10** and **B-3**
24		5-bromo-1-(2-hydroxyethyl)-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 523.1 Found 523.0	**A-3**
25		1'-[2-(4-methanesulfonylphenoxy)ethyl]-1-(2-methoxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 484.2 Found 484.2	**A-3** and **B-8**

Example 9

1-(2-(4-(methylsulfonyl)phenoxy)ethyl)spiro[azepane-4,3'-indolin]-2'-one (Compound 26)

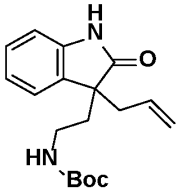


Step 1: *tert*-butyl N-[2-(2-oxo-2,3-dihydro-1H-indol-3-yl)ethyl]carbamate



[1046] To a solution of 2-(1H-indol-3-yl)ethan-1-amine (15 g, 93.6 mmol) in AcOH (90 mL) was added a solution of 12.0 M aqueous HCl (45 mL, 540 mmol) in DMSO (15 mL) dropwise. The mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with H_2O (200 mL) and adjusted to pH = 8 with the addition of solid Na_2CO_3. Boc_2O (21.8 g, 99.9 mmol) was added, and the mixture was stirred at room temperature for 16 h. The reaction mixture was filtered to give a crude product, which was isolated as a solid. The crude product was triturated with 4:1 petroleum ether: EtOAc and filtered to give *tert*-butyl *N*-[2-(2-oxo-2,3-dihydro-1H-indol-3-yl)ethyl]carbamate. MS = 177.1 $[M–C_5H_8O_2+H]^+$.

Step 2: *tert*-butyl *N*-{2-[2-oxo-3-(prop-2-en-1-yl)-2,3-dihydro-1H-indol-3-yl]ethyl}carbamate



[1047] To a 0 °C solution of *tert*-butyl *N*-[2-(2-oxo-2,3-dihydro-1H-indol-3-yl)ethyl]carbamate (4.50 g, 16.3 mmol) in DMA (60 mL) was added NaH (782 mg, 60 wt% in mineral oil, 19.5 mmol). After stirring for 30 min, 3-bromoprop-1-ene (1.97 g, 16.3 mmol) was added dropwise. The mixture was stirred at room temperature for 2.5 h. The reaction mixture was cooled to 0 °C and quenched by the addition of H_2O (20 mL), and then was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 40 g

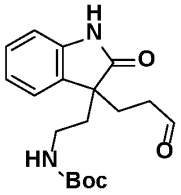
cartridge, 0–18% EtOAc:petroleum ether) to give *tert*-butyl *N*-{2-[2-oxo-3-(prop-2-en-1-yl)-2,3-dihydro-1H-indol-3-yl]ethyl}carbamate. MS = 217.1 $[M–C_5H_8O_2+H]^+$.

Step 3: *tert*-butyl *N*-{2-[3-(3-hydroxypropyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]ethyl}carbamate



[1048] To a 0 °C solution of *tert*-butyl *N*-{2-[2-oxo-3-(prop-2-en-1-yl)-2,3-dihydro-1H-indol-3-yl]ethyl}carbamate (4.10 g, 13.0 mmol) in THF (50 mL) was added 1.0 M BH_3•THF in THF (38.9 mL, 38.9 mmol) dropwise. The mixture was stirred at 0 °C for 2 h under N_2 atmosphere. The reaction mixture was quenched by the addition of H_2O (30 mL) at 0 °C, and then NaOH (1.04 g, 25.9 mmol) and H_2O_2 in H_2O (5.27 mL, 30 wt%, 54.9 mmol) was added. The mixture was stirred at room temperature for 14 h. The reaction mixture was cooled to 0 °C and quenched by the addition of saturated aqueous Na_2SO_3 (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with saturated aqueous Na_2SO_3 (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 40 g cartridge, 0–100% EtOAc:petroleum ether) to give *tert*-butyl *N*-{2-[3-(3-hydroxypropyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]ethyl}carbamate. MS = 235.2 $[M–C_5H_8O_2+H]^+$.

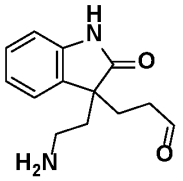
Step 4: *tert*-butyl *N*-{2-[2-oxo-3-(3-oxopropyl)-2,3-dihydro-1H-indol-3-yl]ethyl}carbamate



[1049] To a –78°C solution of $(COCl)_2$ (825 µL, 9.42 mmol) in DCM (50 mL) was added DMSO (981 µL, 12.6 mmol) dropwise followed by *tert*-butyl *N*-{2-[3-(3-hydroxypropyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]ethyl}carbamate (2.10 g, 6.28 mmol). After 30 min, TEA (2.62 mL, 18.8 mmol) was added. The mixture was warmed up to room temperature and stirred for 30 min. The reaction mixture was diluted with H_2O (20 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give crude

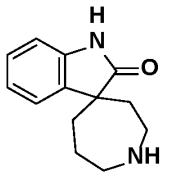
tert-butyl *N*-{2-[2-oxo-3-(3-oxopropyl)-2,3-dihydro-1H-indol-3-yl]ethyl}carbamate, which was used in the subsequent step without further purification. MS = 233.1 $[M–C_5H_8O_2+H]^+$.

Step 5: 3-[3-(2-aminoethyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]propanal



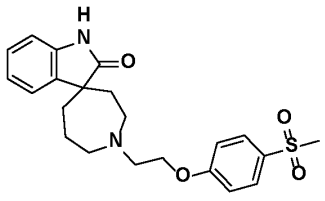
[1050] To a solution of *tert*-butyl *N*-{2-[2-oxo-3-(3-oxopropyl)-2,3-dihydro-1H-indol-3-yl]ethyl}carbamate (600 mg, 1.81 mmol) in DCM (20 mL) was added TFA (10.0 mL, 135 mmol). The mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated in vacuo to give 3-[3-(2-aminoethyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]propanal, which was used in the subsequent step without further purification. MS = 233.1 $[M+H]^+$.

Step 6: 1',2'-dihydrospiro[azepane-4,3'-indol]-2'-one



[1051] A solution of 3-[3-(2-aminoethyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]propanal (1.81 mmol, TFA salt) in MeOH (20 mL) was adjusted to pH = 6 by the dropwise addition of TEA. Then $NaBH_3CN$ (210 mg, 3.35 mmol) was added, and the mixture was stirred at room temperature for 16 h. The reaction mixture cooled to 0 °C and was quenched by the addition H_2O (10 mL) and was then concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters Xbridge BEH C_{18} column, 1–30% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 1',2'-dihydrospiro[azepane-4,3'-indol]-2'-one. MS = 217.1 $[M+H]^+$.

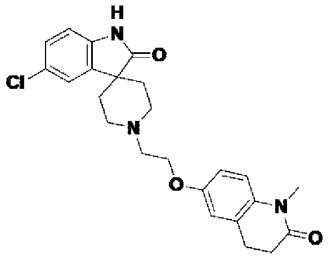
Step 7: 1-(2-(4-(methylsulfonyl)phenoxy)ethyl)spiro[azepane-4,3'-indolin]-2'-one (Compound 26)



[1052] A 70 °C solution of spiro[azepane-4,3'-indoline]-2'-one (50.0 mg, 0.231 mmol), 1-(2-bromoethoxy)-4-methanesulfonylbenzene (**Intermediate A-3**, 64.5 mg, 0.231 mmol) and K_2CO_3 (63.9 mg, 0.462 mmol) in MeCN (5 mL) was stirred for 10 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters Welch Xtimate C_{18} column, 5–25% MeCN: 0.04% HCl in H_2O) to give 1-(2-(4-(methylsulfonyl)phenoxy)ethyl)spiro[azepane-4,3'-indolin]-2'-one (**Compound 26,** HCl salt). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.08 (s, 1H), 10.52–10.46 (m, 1H), 7.91–7.88 (m, 2H), 7.52–7.40 (m, 1H), 7.25 (d, J = 8.8 Hz, 2H), 7.23–7.18 (m, 1H), 7.00 (t, J = 7.6 Hz, 1H), 6.86 (d, J = 7.6 Hz, 1H), 4.59–4.54 (m, 2H), 3.92–3.80 (m, 1H), 3.67–3.60 (m, 4H), 3.36–3.34 (m, 1H), 3.17 (s, 3H), 2.43–2.38 (m, 1H), 2.22–1.88 (m, 5H). MS = 415.2 $[M+H]^+$.

Example 10

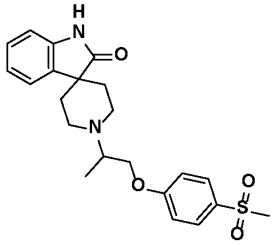
5-chloro-1'-[2-[(1-methyl-2-oxo-3,4-dihydroquinolin-6-yl)oxy]ethyl]spiro[indoline-3,4'-piperidine]-2-one (Compound 27)



[1053] To a solution of 6-hydroxy-1-methyl-1,2,3,4-tetrahydroquinolin-2-one (**Intermediate A-70**, 50.0 mg, 0.282 mmol) and 5-chloro-1'-(2-chloroethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-5**, 169 mg, 0.564 mmol) in DMF (1 mL) was added K_2CO_3 (78.9 mg, 0.564 mmol). The mixture was stirred at 50 °C for 12 h under N_2 atmosphere, cooled to room temperature, and then filtered. The filtrate was purified by reverse phase preparative HPLC (Phenomenex Luna C_{18} column, 5–25% MeCN: 0.04% HCl in H_2O) to give 5-chloro-1'-[2-[(1-methyl-2-oxo-3,4-dihydroquinolin-6-yl)oxy]ethyl]spiro[indoline-3,4'-piperidine]-2-one (**Compound 27**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.53–10.49 (m, 1H), 7.50 (s, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.00 (d, J = 8.8 Hz, 1H), 6.88–6.83 (m, 3H), 4.10 (t, J = 5.6 Hz, 2H), 3.22 (s, 3H), 2.91–2.78 (m, 6H), 2.67–2.64 (m, 2H), 2.44–2.42 (m, 2H), 1.83–1.66 (m, 4H). MS = 440.3 $[M+H]^+$.

Example 11

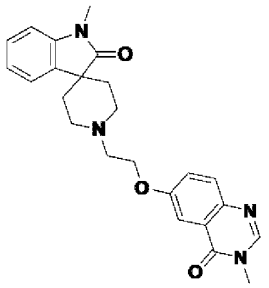
1'-(1-(4-(methylsulfonyl)phenoxy)propan-2-yl)spiro[indoline-3,4'-piperidin]-2-one (Compound 28)



[1054] A 50 °C mixture of 1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (150 mg, 0.742 mmol), 1-(4-methanesulfonylphenoxy)propan-2-one (**Intermediate A-1**, 169 mg, 0.742 mmol), Ti(*i*-PrO)$_4$ (211 mg, 0.742 mmol) and HOAc (4.0 mg, 0.074 mmol) in DCE (5 mL) was stirred for 30 min. After cooling to 0 °C, NaBH(OAc)$_3$ (236 mg, 1.11 mmol) was added. The mixture was stirred at 50 °C for 16 h. After cooling to room temperature, the reaction mixture was quenched with addition of H_2O (10 mL). The mixture was filtered, and the filtrate was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex Gemini NX-C$_{18}$, 10–50% MeCN:10 mM NH_4HCO_3 in H_2O) to give 1'-(1-(4-(methylsulfonyl)phenoxy)propan-2-yl)spiro[indoline-3,4'-piperidin]-2-one (**Compound 28**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.34 (s, 1H), 7.87–7.84 (m, 2H), 7.43–7.41 (m, 1H), 7.23–7.15 (m, 3H), 6.94–6.92 (m, 1H), 6.85–6.83 (m, 1H), 4.27–4.23 (m, 1H), 4.09–4.05 (m, 1H), 3.16 (s, 3H), 3.15–3.13 (m, 1H), 3.00–2.97 (m, 2H), 2.86–2.78 (m, 2H), 1.79–1.77 (m, 2H), 1.61–1.58 (m, 2H), 1.16 (d, J = 6.4 Hz, 3H). MS = 415.0 $[M+H]^+$.

Example 12

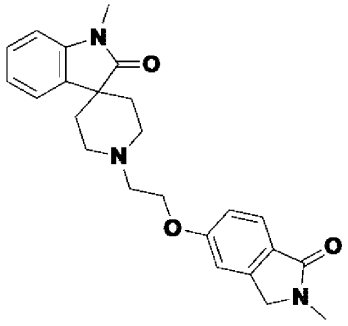
1-methyl-1'-{2-[(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 29)

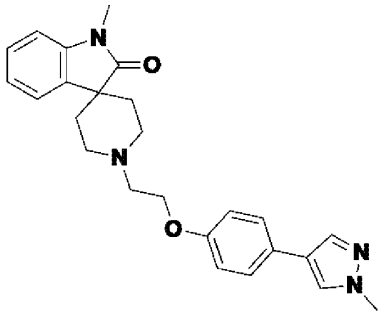
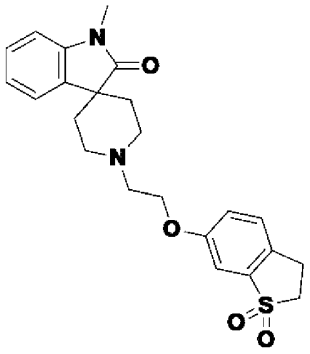
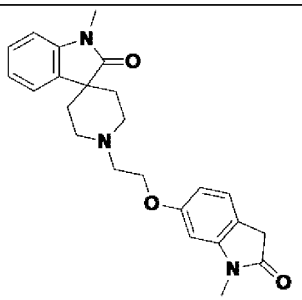
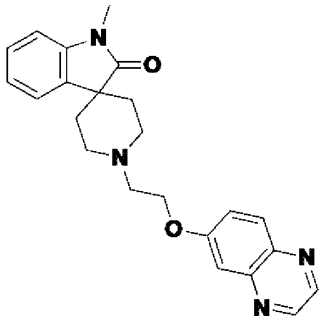


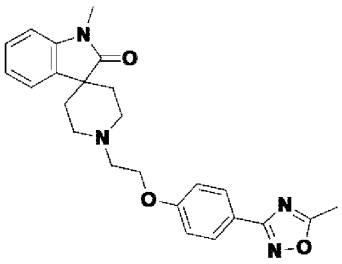
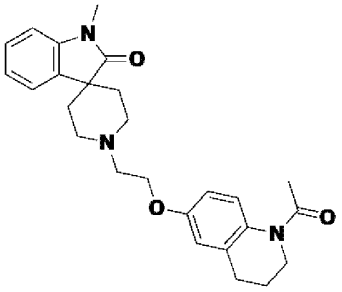
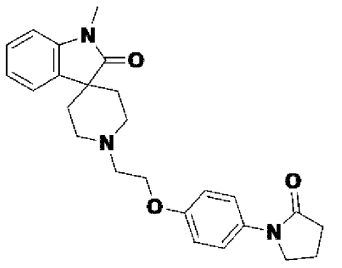
[1055] 1'-(2-hydroxyethyl)-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-7**, 130 mg, 0.50 mmol) and 6-hydroxy-3-methyl-3,4-dihydroquinazolin-4-one (88 mg, 0.50 mmol) were added to a 40 mL vial, followed by toluene (2.00 mL), polymer-bound PPh_3 (167 mg, 78.6% PPh_3 loading by weight, 0.500 mmol) and DIAD (120 mg, 0.600 mmol). The mixture was stirred at room temperature for 12 h, then was filtered and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex Gemini NX-C_{18}, 0–50% MeCN: 10 mM NH_4OH in H_2O) to give 1'-(1-(4-(methylsulfonyl)phenoxy)propan-2-yl)spiro[indoline-3,4'-piperidin]-2-one (**Compound 29**). ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.71 (d, J = 2.85 Hz, 1H), 7.65 (d, J = 8.99 Hz, 1H), 7.39 (dd, J = 8.88, 2.74 Hz, 2H), 7.27–7.31 (m, 1H), 7.00–7.12 (m, 1H), 6.84 (d, J = 7.67 Hz, 1H), 4.23–4.42 (m, 2H), 3.60 (s, 3H), 3.20 (s, 3H), 3.00–3.19 (m, 4H), 2.81–3.00 (m, 2H), 1.81–2.06 (m, 4H). MS = 419.2 $[M+H]^+$.

[1056] The following compounds in Table 21 were prepared according to procedures similar to those described for **Compound 29** using the appropriate starting materials.

Table 21.

#	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Intermediate Used
30		1-methyl-1'-{2-[(2-methyl-1-oxo-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 406.2 Found 406.2	**B-7**

31		1-methyl-1'-{2-[4-(1-methyl-1H-pyrazol-4-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 417.2 Found 417.2	**B-7**
32		5-(2-{1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,3-dihydro-1λ⁶-benzothiophene-1,1-dione	Calc'd 427.1 Found 427.2	**B-7**
33		1-methyl-1'-{2-[(1-methyl-2-oxo-2,3-dihydro-1H-indol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 406.2 Found 406.2	**B-7**
34		1-methyl-1'-[2-(quinoxalin-6-yloxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 389.1 Found 389.2	**B-7**

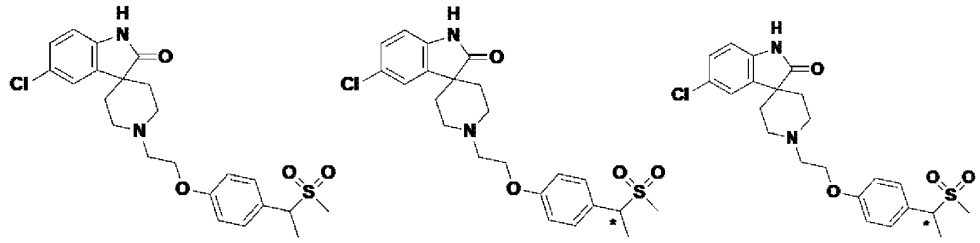
35		1-methyl-1'-{2-[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 419.2 Found 419.2	**B-7**
36		1'-{2-[(1-acetyl-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 434.2 Found 434.3	**B-7**
37		1-methyl-1'-{2-[4-(2-oxopyrrolidin-1-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 420.2 Found 420.2	**B-7**

Example 13

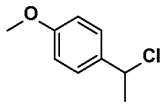
5-chloro-1'-{2-[4-(1-methanesulfonylethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 38),

5-chloro-1'-(2-{4-[(1*S*) or (1*R*)-1-methanesulfonylethyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 39), and

5-chloro-1'-(2-{4-[(1*R*) or (1*S*)-1-methanesulfonylethyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 40)

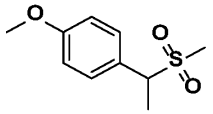


Step 1: 1-(1-chloroethyl)-4-methoxybenzene



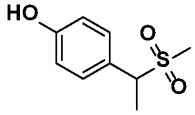
[1057] To a 0 °C solution of 1-(4-methoxyphenyl)ethan-1-ol (5.00 g, 32.9 mmol) in DCM (50 mL) was added $SOCl_2$ (2.86 mL, 39.4 mmol). The mixture was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was concentrated in vacuo to give 1-(1-chloroethyl)-4-methoxybenzene, which was used in the next step without further purification.

Step 2: 1-(1-methanesulfonylethyl)-4-methoxybenzene



[1058] A mixture of 1-(1-chloroethyl)-4-methoxybenzene (6.00 g, 35.1 mmol) and sodium methanesulfinate (7.18 g, 70.3 mmol) in DMF (60 mL) was stirred at 80 °C for 16 h. The mixture was cooled to 0 °C and quenched by the addition of H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with H_2O (50 mL), brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 80 g cartridge, 0–50% EtOAc:petroleum ether) to give 1-(1-methanesulfonylethyl)-4-methoxybenzene. MS = 135.1 $[M–CH_3SO_2]^+$.

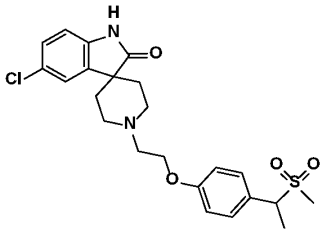
Step 3: 4-(1-methanesulfonylethyl)phenol



[1059] To a solution of 1-(1-methanesulfonylethyl)-4-methoxybenzene (500 mg, 2.33 mmol) in MeCN (5 mL) was added NaI (1.40 g, 9.33 mmol) and TMSCl (1.18 mL, 9.33 mmol). The mixture

was stirred at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was quenched by the addition of H_2O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$ (60 mL), brine (60 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 25–50% EtOAc:petroleum ether) to give 4-(1-methanesulfonylethyl)phenol. MS = 218.2 $[M+NH_4]^+$.

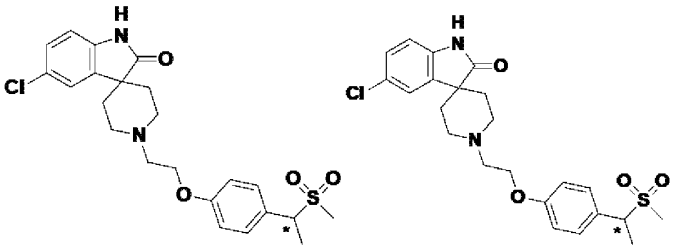
Step 4: 5-chloro-1'-{2-[4-(1-methanesulfonylethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 38)



[1060] To a mixture of 5-chloro-1'-(2-chloroethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-5**, 269 mg, 0.899 mmol) in acetone (10 mL) was added NaI (4.5 mg, 0.030 mmol), K_2CO_3 (82.8 mg, 0.599 mmol) and 4-(1-methanesulfonylethyl)phenol (120 mg, 0.599 mmol). The mixture was stirred at 50 °C for 12 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex Gemini NX-C_{18}, 20–50% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-{2-[4-(1-methanesulfonylethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 38**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 1H), 7.51 (s, 1H), 7.36 (d, J = 8.8 Hz, 2H), 7.23 (m, 1H), 6.99 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.4 Hz, 1H), 4.47 (m 1H), 4.14 (t, J = 5.4 Hz, 2H), 2.91–2.84 (m, 4H), 2.77 (s, 3H), 2.73–2.65 (m, 1H), 1.83–1.67 (m, 5H), 1.59 (d, J = 7.2 Hz, 3H). MS = 463.3 $[M+H]^+$.

Step 5: 5-chloro-1'-(2-{4-[(1*S*) or (1*R*)-1-methanesulfonylethyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 39) and 5-chloro-1'-(2-{4-[(1*R*) or (1*S*)-

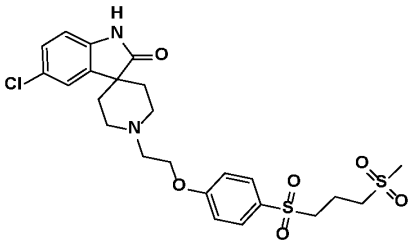
1-methanesulfonylethyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 40)



[1061] 5-chloro-1'-{2-[4-(1-methanesulfonylethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 38**, 45 mg, 0.060 mmol) was separated by preparative chiral SFC (Chiralcel OD-3 column, 60% ethanol with 0.1% NH_4OH in CO_2). The first eluting enantiomer of the title compound, 5-chloro-1'-(2-{4-[(1*S)* or (1*R*)-1-methanesulfonylethyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 39**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.50 (s, 1H), 7.51 (d, J = 2.0 Hz, 1H), 7.36 (d, J = 8.8 Hz, 2H), 7.23 (dd, J = 8.4, 2.2 Hz, 1H), 6.99 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.4 Hz, 1H), 4.47 (q, J = 7.2 Hz, 1H), 4.14 (t, J = 5.6 Hz, 2H), 2.92–2.89 (m, 2H), 2.86–2.83 (m, 2H), 2.77 (s, 3H), 2.71–2.68 (m, 2H), 1.82–1.67 (m, 4H), 1.59 (d, J = 7.2 Hz, 3H). MS = 463.2 $[M+H]^+$. The second eluting enantiomer of the title compound, 5-chloro-1'-(2-{4-[(1*R*) or (1*S*)-1-methanesulfonylethyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 40**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 1H), 7.51 (d, J = 2.0 Hz, 1H), 7.36 (d, J = 8.8 Hz, 2H), 7.23 (dd, J = 8.4, 2.2 Hz, 1H), 6.99 (d, J = 9.0 Hz, 2H), 6.84 (d, J = 8.0 Hz, 1H), 4.47 (q, J = 7.2 Hz, 1H), 4.14 (t, J = 5.6 Hz, 2H), 2.95–2.88 (m, 2H), 2.85 (t, J = 5.6 Hz, 2H), 2.77 (s, 3H), 2.74–2.68 (m, 2H), 1.82–1.68 (m, 4H), 1.60 (d, J = 7.2 Hz, 3H). MS = 463.2 $[M+H]^+$.

Example 14

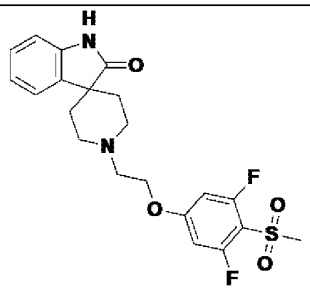
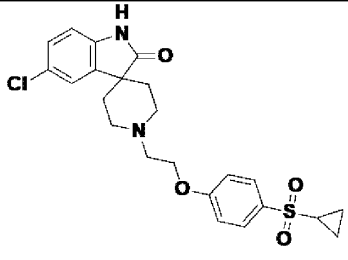
5-chloro-1'-{2-[4-(3-methanesulfonylpropanesulfonyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 41)

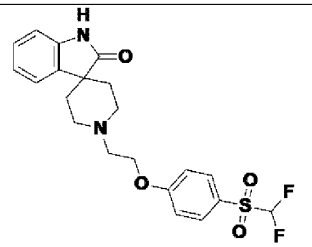


[1062] To a solution of 4-(3-methanesulfonylpropanesulfonyl)phenol (**Intermediate A-9**, 60.0 mg, 0.216 mmol) in DMF (2 mL) was added K_2CO_3 (59.6 mg, 0.431 mmol) and 5-chloro-1'-(2-chloroethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-5**, 129 mg, 0.431 mmol). The mixture was stirred at 50 °C for 12 h. The reaction mixture was filtered and the filtrate was purified by reverse phase preparative HPLC (Waters Xbridge BEH C_{18} column, 20–55% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-{2-[4-(3-methanesulfonylpropanesulfonyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 41**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 7.82 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 2.0 Hz, 1H), 7.25–7.21 (m, 3H), 6.84 (d, J = 8.4 Hz, 1H), 4.26 (t, J = 5.6 Hz, 2H), 3.44–3.37 (m, 2H), 3.24–3.18 (m, 2H), 2.97 (s, 3H), 2.94–2.84 (m, 4H), 2.75–2.70 (m, 2H), 1.99–1.94 (m, 2H), 1.77–1.73 (m, 4H). MS = 541.2 $[M+H]^+$.

[1063] The following compounds in Table 22 were prepared according to procedures similar to those described for **Compound 41** using the appropriate starting materials

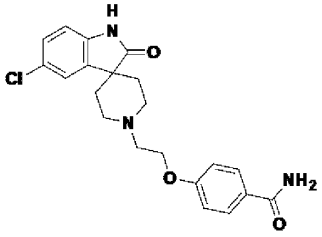
Table 22.

#	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Intermediates Used
42		1'-[2-(3,5-difluoro-4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 437.1 Found 437.0	**A-11** and **B-10**
43		5-chloro-1'-{2-[4-(cyclopropanesulfonyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 461.1 Found 461.1	**B-5**

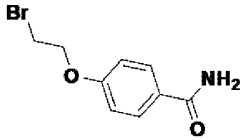
44		1'-[2-(4-difluoromethanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 437.1 Found 437.2	**A-15** and **B-10**

Example 15

4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzamide (Compound 45)

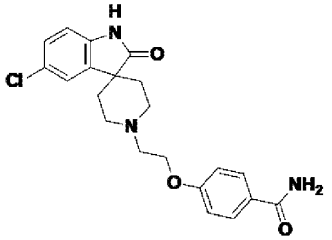


Step 1: 4-(2-bromoethoxy)benzamide



[1064] A mixture of 4-hydroxybenzamide (200 mg, 1.46 mmol), Cs_2CO_3 (950 mg, 2.92 mmol), and 1,2-dibromoethane (2.01 mL, 23.3 mmol) was stirred at 110 °C for 18 h in a sealed vial. After cooling to room temperature, the reaction mixture was diluted with DCM and filtered. The filter cake was then washed with acetone (3 x 5 mL) and the filtrate was concentrated in vacuo to give 4-(2-bromoethoxy)benzamide, which was taken to the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81–7.76 (m, 2H), 6.95 (dd, J = 8.8, 2.2 Hz, 2H), 6.17–5.19 (m, 2H), 4.34 (t, J = 2.0 Hz, 2H), 3.66 (t, J = 2.1 Hz, 2H). MS = 243.9 $[M+H]^+$.

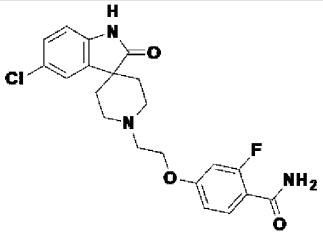
Step 2: 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzamide (Compound 45)

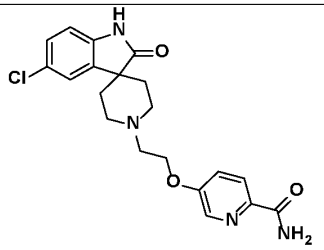
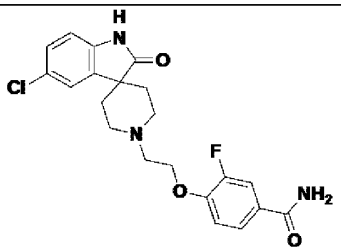
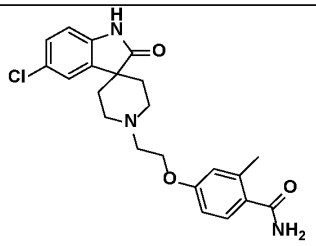


[1065] A mixture of 4-(2-bromoethoxy)benzamide, (36.0 mg, 0.15 mmol), 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 40 mg, 0.15 mmol, HCl salt), and potassium carbonate (61 mg, 0.44 mmol) was taken up in DMF (0.6 mL). The mixture was stirred at 80 °C for 3 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (0.15 mL) and formic acid (3 drops) was added. The mixture was stirred at room temperature for an additional 10 min and solids were removed by filtration. The filtrate was purified reverse phase preparative HPLC (Phenomenex Kinetex C_{18} column, 5–30% MeCN:H_2O with 0.1% formic acid modifier) to give 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzamide (**Compound 45**). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.52 (s, 1H), 7.84–7.78 (m, 3H), 7.51 (s, 1H), 7.25 (d, J = 8.3 Hz, 1H), 7.17 (s, 1H), 7.02 (d, J = 8.3 Hz, 2H), 6.85 (d, J = 8.3 Hz, 1H), 4.23 (s, 2H), 3.15–2.66 (m, 6H), 2.13–1.60 (m, 4H). MS = 400.1 $[M+H]^+$.

[1066] The following compounds in Table 23 were prepared according to procedures analogous to steps 1–2 described for **Compound 45** using the appropriate starting materials.

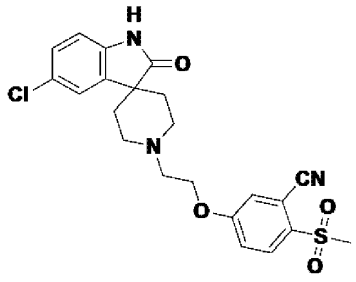
Table 23.

#	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Intermediate Used
46		4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzamide	Calc'd 418.1 Found 418.1	**B-4**

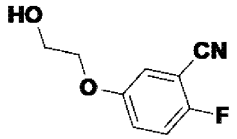
47		5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)pyridine-2-carboxamide	Calc'd 401.1 Found 401.2	**B-4**
48		5-chloro-1'-[2-(2-fluoro-4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 453.1 Found 453.0	**B-4**
49		4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-methylbenzamide	Calc'd 414.2 Found 414.2	**B-4**

Example 16

5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-methanesulfonylbenzonitrile (Compound 50)

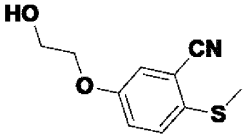


Step 1: 2-fluoro-5-(2-hydroxyethoxy)benzonitrile



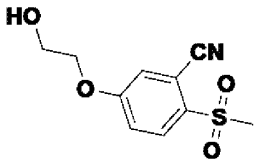
[1067] A mixture of 2-fluoro-5-hydroxybenzonitrile (1.00 g, 7.29 mmol), K_2CO_3 (3.02 g, 21.9 mmol), and ethylene carbonate (20.6 mL, 24.1 mmol) was taken up in DMF (10 mL). The mixture was stirred at 110 °C for 18 hours. After cooling to room temperature, the reaction mixture was filtered to remove solids and concentrated in vacuo. The residue was taken up in EtOAc (15 mL), and then washed with H_2O (5 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to give 2-fluoro-5-(2-hydroxyethoxy)benzonitrile, which was taken to the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18–7.11 (m, 2H), 7.10 (dd, *J* = 5.2, 2.5 Hz, 1H), 4.10–4.04 (m, 2H), 3.98 (t, *J* = 4.4 Hz, 2H), 1.98 (s, 1H).

Step 2: 5-(2-hydroxyethoxy)-2-(methylsulfanyl)benzonitrile



[1068] A mixture of 2-fluoro-5-(2-hydroxyethoxy)benzonitrile (875 mg, 4.83 mmol), aqueous sodium methanethiolate (6.77 g, 15 wt%, 14.5 mmol), and DMF (6.7 mL) was stirred at 60 °C for 18 h. After cooling to room temperature, the reaction mixture was diluted with brine (10 mL) and extracted EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give 5-(2-hydroxyethoxy)-2-(methylsulfanyl)benzonitrile, which was taken to the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$, 10/11 H): δ 7.36 (d, *J* = 8.8 Hz, 1H), 7.15 (d, *J* = 2.8 Hz, 1H), 7.11 (dd, *J* = 8.8, 2.8 Hz, 1H), 4.08 (dd, *J* = 5.1, 3.8 Hz, 2H), 3.98 (t, *J* = 4.4 Hz, 2H), 2.52 (s, 3H).

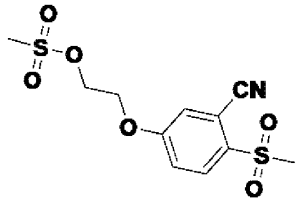
Step 3: 5-(2-hydroxyethoxy)-2-methanesulfonylbenzonitrile



[1069] To a 0 °C suspension of 5-(2-hydroxyethoxy)-2-(methylsulfanyl)benzonitrile (169 mg, 0.808 mmol) in DCM (3 mL) was added *m*-CPBA (432 mg, 2.50 mmol) in a single portion. The

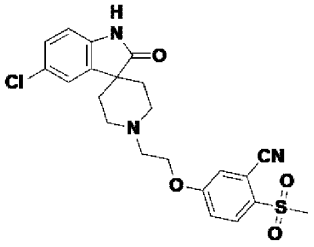
mixture was allowed to slowly warm to room temperature and stirred for 18 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (10 mL) and allowed to stir for an additional 15 min. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 10 g cartridge, 0–100% EtOAc:Hexanes) to give 5-(2-hydroxyethoxy)-2-methanesulfonylbenzonitrile. ^1H NMR (500 MHz, $CDCl_3$, 10/11 H): δ 8.12 (d, J = 8.9 Hz, 1H), 7.43 (s, 1H), 7.30 (dd, J = 9.0, 2.6 Hz, 1H), 4.24 (t, J = 4.4 Hz, 2H), 4.07 (t, J = 4.5 Hz, 2H), 3.27 (s, 3H).

Step 4: 2-(3-cyano-4-methanesulfonylphenoxy)ethyl methanesulfonate



[1070] Methanesulfonyl chloride (70 μL, 0.82 mmol) was added dropwise via syringe to a 0 °C solution of 5-(2-hydroxyethoxy)-2-methanesulfonylbenzonitrile (132 mg, 0.548 mmol) and DIEA (0.19 mL, 0.82 mmol) in DCM (2 mL). The mixture was allowed to slowly warm to room temperature and stirred for 3 h. The reaction mixture was diluted with saturated aqueous NH_4Cl (5 mL) and stirred for an additional 15 min. The organic layer was separated, and the aqueous layer was extracted with DCM (3 x 2 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give 2-(3-cyano-4-methanesulfonylphenoxy)ethyl methanesulfonate, which was taken to the next step without further purification.

Step 5: 5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-methanesulfonylbenzonitrile (Compound 50)

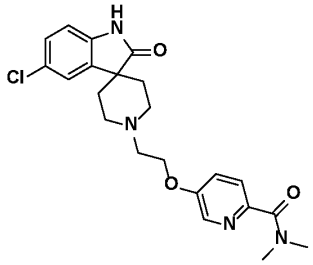


[1071] A mixture of 2-(3-cyano-4-methanesulfonylphenoxy)ethyl methanesulfonate (51.0 mg, 0.16 mmol), 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 40.0 mg, 0.146 mmol, HCl salt) and K_2CO_3 (50.6 mg, 0.366 mmol), in DMF (0.6 mL) was stirred at 80 °C for 3 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (0.15 mL) and purified by reverse phase preparative HPLC (Phenomenex Kinetex C_{18} column, 10–30% MeCN:H_2O with 0.1% formic acid modifier) to give 5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-methanesulfonylbenzonitrile (**Compound 50**). ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 10.49 (s, 1H), 8.02 (d, *J* = 8.9 Hz, 1H), 7.83 (d, *J* = 2.6 Hz, 1H), 7.58–7.44 (m, 2H), 7.23 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 4.34 (t, *J* = 5.6 Hz, 2H), 3.11 (br s, 3H), 2.97–2.83 (m, 4H), 2.74–2.65 (m, 2H), 1.83–1.74 (m, 2H), 1.74–1.61 (m, 2H). MS = 460.0 [M+H]+.

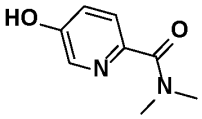
[1072]

Example 17

4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-methylbenzamide (Compound 51)



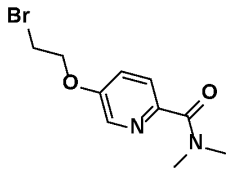
Step 1: 5-hydroxy-*N*,*N*-dimethylpyridine-2-carboxamide



[1073] To a mixture of 5-hydroxypyridine-2-carboxylic acid (500 mg, 3.59 mmol) and dimethylamine hydrochloride (440 mg, 5.40 mmol) in DMF (2.5 mL) was added DIEA (1.88 mL, 10.8 mmol). The mixture was stirred for 10 min, then HATU (1.64 g, 4.3 mmol) was added in a single portion. After stirring for 18 h, the reaction mixture was diluted with brine (5 mL) and filtered to remove solids. The filtrate was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by

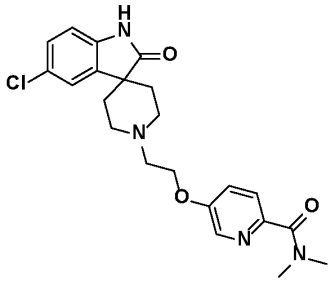
normal phase silica gel chromatography (Biotage 10 g cartridge, 0–20% MeOH:DCM) to give 5-hydroxy-*N,N*-dimethylpyridine-2-carboxamide. ^{1}H NMR (500 MHz, $CDCl_3$, 9/10 H): δ 8.07 (d, *J* = 2.8 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 1H), 7.08 (dd, *J* = 8.5, 2.8 Hz, 1H), 3.14–3.07 (m, 6H).

Step 2: 5-(2-bromoethoxy)-*N,N*-dimethylpyridine-2-carboxamide



[1074] A mixture of 5-hydroxy-*N,N*-dimethylpyridine-2-carboxamide (158 mg, 0.951 mmol) and Cs_2CO_3 (620 mg, 1.90 mmol) in 1,2-dibromoethane (1.24 mL, 14.3 mmol) was stirred at 110 °C for 18 h in a sealed vial. After cooling to room temperature, the reaction mixture was diluted with DCM and filtered to remove solids. The filter cake was then washed with DCM (3 x 5 mL) and concentrated under reduced pressure to give 5-(2-bromoethoxy)-*N,N*-dimethylpyridine-2-carboxamide, which was taken to the next step without further purification. ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 8.30 (s, 1H), 7.60–7.53 (m, 1H), 7.53–7.48 (m, 1H), 4.46 (t, *J* = 4.5 Hz, 2H), 3.84 (t, *J* = 4.3 Hz, 2H), 2.99 (s, 6H).

Step 3: 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-methylbenzamide (Compound 51)

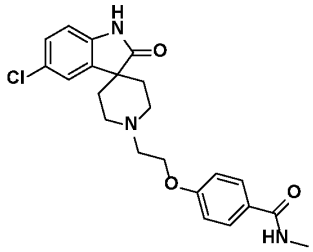


[1075] A mixture of 5-(2-bromoethoxy)-*N,N*-dimethylpyridine-2-carboxamide (25.0 mg, 0.0915 mmol), 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 25.0 mg, 0.0915 mmol, HCl salt), K_2CO_3 (31.6 mg, 0.229 mmol), and KI (15.0 mg, 0.0904 mmol) in DMF (0.6 mL) was stirred at 75 °C for 3 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (0.15 mL) and purified by reverse phase preparative HPLC (Phenomenex Kinetex C_{18} column, 10–30% MeCN:H_2O with 0.1% formic acid modifier) to give 4-(2-{5-chloro-2-oxo-1,2-

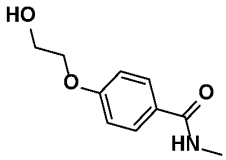
dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-methylbenzamide (**Compound 51**). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.49 (s, 1H), 8.29 (d, J = 2.7 Hz, 1H), 7.57 (d, J = 8.6 Hz, 1H), 7.54–7.48 (m, 2H), 7.23 (dd, J = 8.2, 2.1 Hz, 1H), 6.84 (d, J = 8.3 Hz, 1H), 4.27 (t, J = 5.7 Hz, 2H), 3.00 (s, 3H), 2.99 (s, 3H), 2.97–2.90 (m, 2H), 2.88 (t, J = 5.7 Hz, 2H), 2.75–2.66 (m, 2H), 1.86–1.75 (m, 2H), 1.75–1.64 (m, 2H). MS = 429.1 $[M+H]^+$.

Example 18

4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-methylbenzamide (Compound 52)

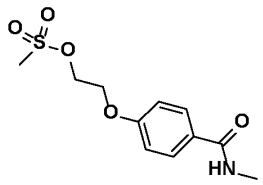


Step 1: 4-(2-hydroxyethoxy)-*N*-methylbenzamide



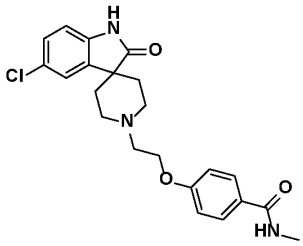
[1076] To a mixture of 4-(2-hydroxyethoxy)benzoic acid (500 mg, 2.75 mmol) and methylamine hydrochloride (278 mg, 4.12 mmol) in a solution of 10:1 THF/DMF (5.5 mL) was added DIEA (1.43 mL, 8.2 mmol). The mixture was stirred at room temperature for 10 min. HATU (1.25 g, 3.3 mmol) was added in a single portion and stirring was continued for 18 h. The reaction mixture was diluted with brine (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 10 g cartridge, 0–10% MeOH:DCM) to give 4-(2-hydroxyethoxy)-*N*-methylbenzamide. MS = 196.1 $[M+H]^+$.

Step 2: 2-[4-(methylcarbamoyl)phenoxy]ethyl methanesulfonate



[1077] Methanesulfonyl chloride (0.45 mL, 2.9 mmol) was added dropwise to a 0 °C solution of 4-(2-hydroxyethoxy)-*N*-methylbenzamide (380 mg, 1.95 mmol) and DIEA (0.300 mL, 3.41 mmol) in DCM (4 mL). The mixture was allowed to slowly warm to room temperature and stirring was continued 16 h. The reaction mixture was diluted with saturated aqueous NH_4Cl (5 mL) and allowed to stir an additional 15 min. The organic layer was separated, and the aqueous layer was extracted with DCM (3 x 2 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 10 g cartridge, 0–10% MeOH:DCM) to give 2-[4-(methylcarbamoyl)phenoxy]ethyl methanesulfonate. MS = 274.1 $[M+H]^+$.

Step 3: 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-methylbenzamide (Compound 52)

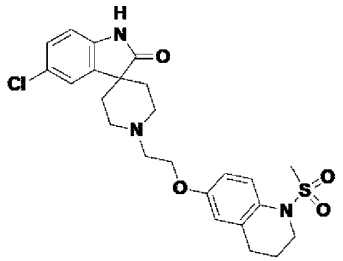


[1078] A mixture of 2-[4-(methylcarbamoyl)phenoxy]ethyl methanesulfonate (30.0 mg, 0.110 mmol), 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 30.0 mg, 0.110 mmol, HCl salt), K_2CO_3 (37.9 mg, 0.274 mmol), and KI (18.2 mg, 0.110 mmol) in DMF (0.6 mL) was stirred at 75 °C for 5 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (0.2 mL) and 5 drops of formic acid was added. The mixture was purified by reverse phase preparative HPLC (Phenomenex Kinetex C_{18} column, 10–30% MeCN:H_2O with 0.1% formic acid modifier) to give 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-methylbenzamide (**Compound 52**). ^1H NMR (500 MHz, DMSO-d_6): δ 10.53 (s, 1H), 8.35–8.19 (m, 1H), 7.80 (d, J = 10.0, 2H), 7.52 (s, 1H), 7.24 (dd, J = 8.3, 2.1 Hz, 1H), 7.02 (d, J = 10.0, 2H),

6.85 (d, J = 8.3 Hz, 1H), 4.23 (t, J = 5.6 Hz, 2H), 3.04–3.00 (m, 4H) 2.83 (br s, 2H), 2.76 (d, J = 4.4 Hz, 3H), 1.99–1.58 (m, 4H). MS = 414.2 $[M+H]^+$.

Example 19

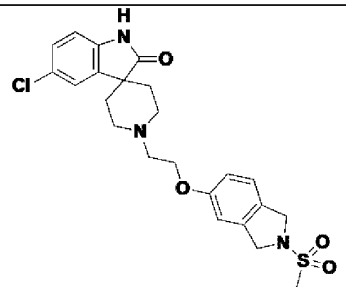
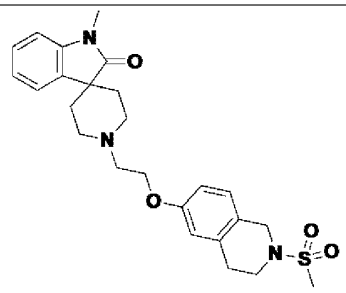
5-chloro-1'-{2-[(1-methanesulfonyl-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 53)



[1079] To a 0 °C solution of *tert*-butyl 6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-1,2,3,4-tetrahydroquinoline-1-carboxylate (**Intermediate C-1**, 84.0 g, 0.173 mmol, HCl salt) in DCM (1.73 mL) was added TEA (0.121 mL, 0.865 mmol), followed by methanesulfonyl chloride (20.1 µL, 0.260 mmol) dropwise. The mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with DCM (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex Kinetex C_{18} column, 0–50% MeCN:H_2O with 0.1% formic acid modifier) to give 5-chloro-1'-{2-[(1-methanesulfonyl-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 53**). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.49 (s, 1H), 7.51 (d, J = 2.0 Hz, 1H), 7.43 (d, J = 8.6 Hz, 1H), 7.24 (d, J = 8.2 Hz, 1H), 6.85 (d, J = 8.3 Hz, 1H), 6.80 (d, J = 8.9 Hz, 2H), 4.11 (t, J = 5.7 Hz, 2H), 3.66 (t, J = 4.9 Hz, 2H), 2.97–2.89 (m, 5H), 2.86 (t, J = 5.8 Hz, 2H), 2.78 (t, J = 6.7 Hz, 2H), 2.75–2.67 (m, 2H), 1.96–1.86 (m, 2H), 1.83–1.70 (m, 4H). MS = 490.2 $[M+H]^+$.

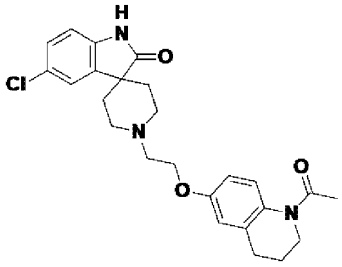
[1080] The following compounds in Table 24 were prepared according to procedures analogous to those described for **Compound 53** using the appropriate starting materials.

Table 24.

#	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Inter-mediates Used
54		5-chloro-1'-{2-[(2-methanesulfonyl-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 476.1 Found 476.1	**C-2**
55		1'-{2-[(2-methanesulfonyl-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy]ethyl}-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 470.2 Found 470.2	**C-5**

Example 20

1'-{2-[(1-acetyl-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 56)

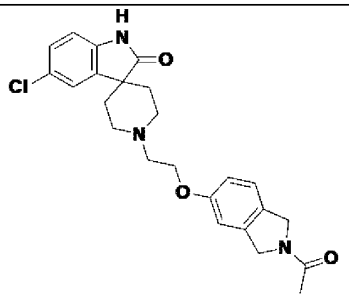
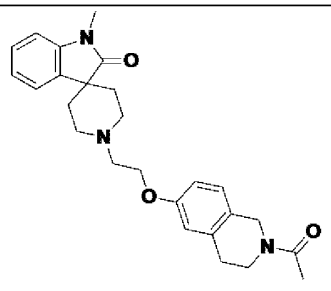


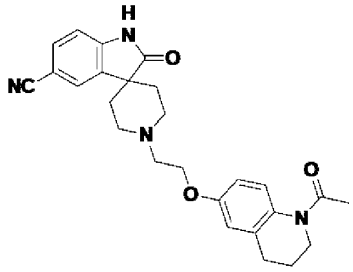
[1081] To a 0 °C solution of *tert*-butyl 6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-1,2,3,4-tetrahydroquinoline-1-carboxylate (**Intermediate C-1**, 84.0 mg, 0.173 mmol, HCl salt) in DCM (1.73 mL) was added TEA (0.121 mL, 0.865 mmol), followed

by acetic anhydride (23.9 μL, 0.260 mmol) dropwise. The mixture was stirred for 30 min and was then diluted with H_2O (10 mL) and extracted with DCM (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex Kinetex C_{18} column, 0–40% MeCN:H_2O with 0.1% formic acid modifier) to give 1'-{2-[(1-acetyl-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 56**). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.49 (s, 1H), 8.15 (s, 1H), 7.51 (d, J = 2.1 Hz, 1H), 7.24 (dd, J = 8.2, 2.1 Hz, 1H), 6.85 (d, J = 8.3 Hz, 1H), 6.83–6.75 (m, 2H), 4.12 (t, J = 5.8 Hz, 2H), 3.64 (t, J = 6.4 Hz, 2H), 2.98–2.89 (m, 2H), 2.86 (t, J = 5.8 Hz, 2H), 2.75–2.66 (m, 4H), 2.11 (s, 3H), 1.88–1.68 (m, 6H). MS = 454.1 $[M+H]^+$.

[1082] The following compounds in Table 25 were prepared according to procedures analogous to those described for **Compound 56** using the appropriate starting materials.

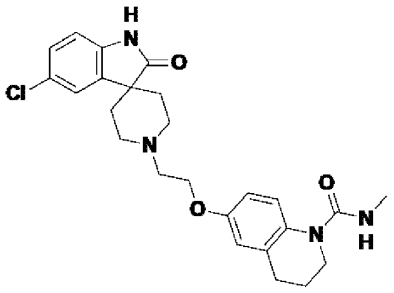
Table 25.

#	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Inter-mediates Used
57		1'-{2-[(2-acetyl-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 440.2 Found 440.1	**C-2**
58		1'-{2-[(2-acetyl-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy]ethyl}-1-methyl-1,2-dihydrospiro[indole	Calc'd 434.2 Found 434.1	**C-5**

		-3,4'-piperidin]-2-one		
59		1'-{2-[(1-acetyl-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 445.2 Found 445.2	**C-4**

Example 21

6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-methyl-1,2,3,4-tetrahydroquinoline-1-carboxamide (Compound 60)

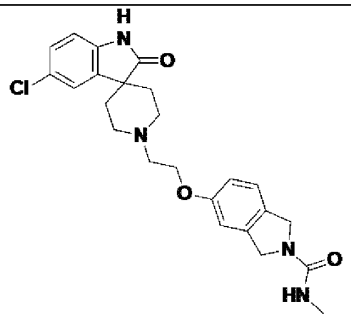


[1083] To a 0 °C mixture of 5-chloro-1'-[2-(1,2,3,4-tetrahydroquinolin-6-yloxy)ethyl]-1H-spiro[indole-3,4'-piperidin]-2-one (**Intermediate C-1**, 0.118 g, 0.244 mmol) in DCM (1.6 mL) was added TEA (0.134 mL, 0.976 mmol), followed by *N*-methylcarbamoyl chloride (0.034 g, 0.366 mmol). The mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL) and extracted with DCM (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex Kinetex C_{18} column,

0–40% MeCN:H_2O with 0.1% formic acid modifier) to give 6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-methyl-1,2,3,4-tetrahydroquinoline-1-carboxamide (**Compound 60**). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.49 (s, 1H), 7.52 (s, 1H), 7.30 (d, J = 8.6 Hz, 1H), 7.27–7.21 (m, 1H), 6.85 (dd, J = 8.3, 1.5 Hz, 1H), 6.73 (d, J = 8.2 Hz, 2H), 6.40 (q, J = 4.6 Hz, 1H), 4.09 (t, J = 5.8 Hz, 2H), 3.52 (t, J = 6.2 Hz, 2H), 2.98–2.89 (m, 2H), 2.85 (t, J = 5.8 Hz, 2H), 2.75–2.68 (m, 2H), 2.66 (t, J = 6.6 Hz, 2H), 2.62 (d, J = 1.5 Hz, 3H), 1.86–1.76 (m, 4H), 1.75–1.68 (m, 2H). MS = 469.1 $[M+H]^+$.

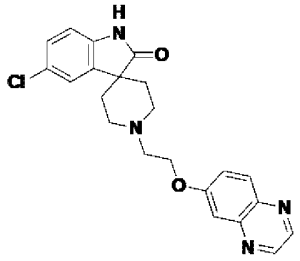
[1084] The following compound in Table 26 was prepared according to procedures analogous to those described for **Compound 60** using the appropriate starting materials.

Table 26.

#	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Inter-mediates Used
61		5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-methyl-2,3-dihydro-1H-isoindole-2-carboxamide	Calc'd 455.2 Found 455.2	**C-2**

Example 22

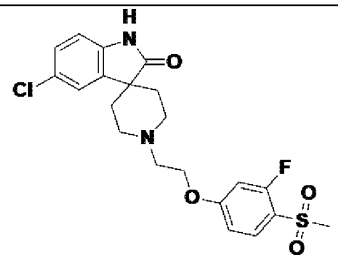
5-chloro-1'-[2-(quinoxalin-6-yloxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 62)

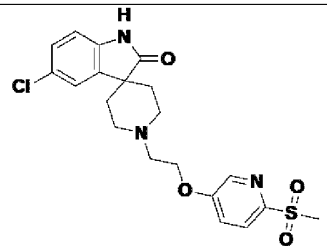


[1085] A mixture of 5-chloro-1'-(2-chloroethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-5**, 40.0 mg, 0.134 mmol), quinoxalin-6-ol (23.4 mg, 0.161 mmol) and K_2CO_3 (27.7 mg, 0.201 mmol) in DMF (1.3 mL) was heated at 80 °C for 1 h. After cooling to room temperature, the mixture was diluted with H_2O (10 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex Kinetex C_{18} column, 0–30% MeCN:H_2O with 0.1% formic acid modifier) to give 5-chloro-1'-[2-(quinoxalin-6-yloxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 62**). ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 10.50 (s, 1H), 8.87 (d, *J* = 2.4 Hz, 1H), 8.78 (d, *J* = 2.4 Hz, 1H), 8.00 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.58–7.49 (m, 3H), 7.23 (d, *J* = 8.3 Hz, 1H), 6.85 (dd, *J* = 8.3, 2.4 Hz, 1H), 4.37 (t, *J* = 5.3 Hz, 2H), 2.98–2.91 (m, 4H), 2.78 (t, *J* = 9.2 Hz, 2H), 1.93–1.67 (m, 4H). MS = 409.1 $[M+H]^+$.

[1086] The following compound in Table 27 was prepared according to procedures analogous to those described for **Compound 62** using the appropriate starting materials.

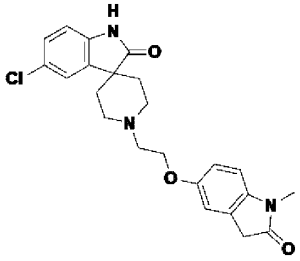
Table 27.

#	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Inter-mediates Used
63		5-chloro-1'-[2-(3-fluoro-4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 453.1 Found 453.1	**B-5**

64		5-chloro-1'-{2-[(6-methanesulfonylpyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 436.1 Found 436.1	**B-5**

Example 23

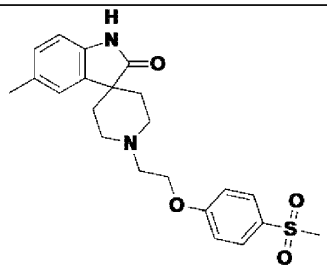
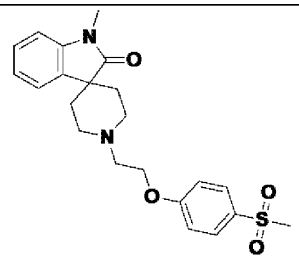
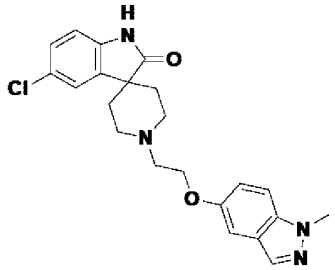
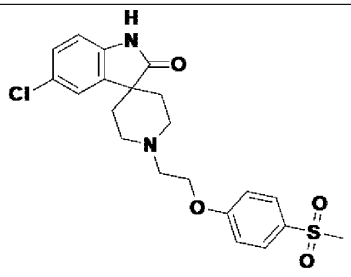
5-chloro-1'-{2-[(1-methyl-2-oxo-2,3-dihydro-1H-indol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 65)

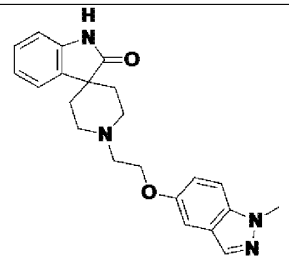
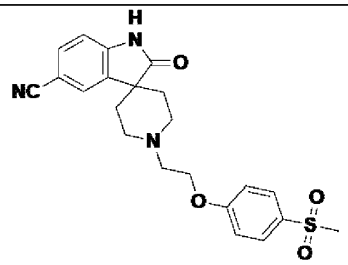
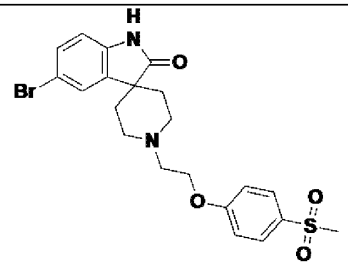
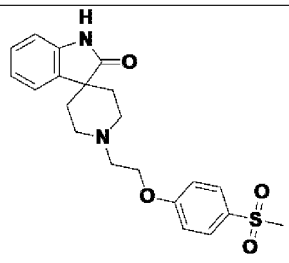
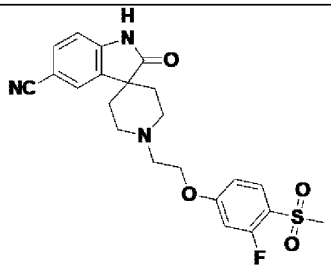


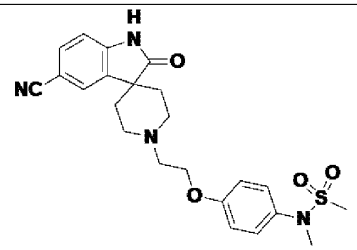
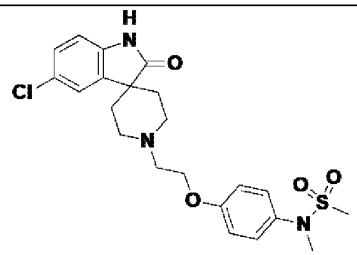
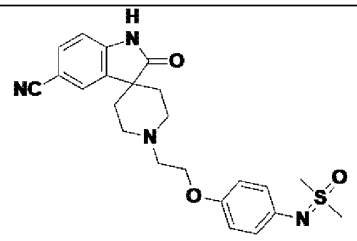
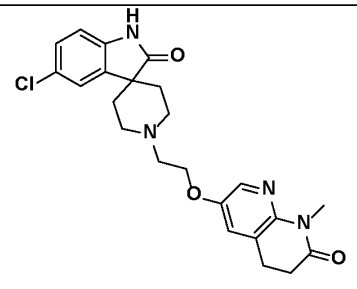
[1087] A mixture of 5-(2-bromoethoxy)-1-methyl-2,3-dihydro-1H-indol-2-one (**Intermediate A-4**, 20 mg, 0.074 mmol), 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 22 mg, 0.081 mmol) and K_2CO_3 (31 mg, 0.22 mmol) in DMF (0.5 mL) was heated at 60 °C for 3 h. After cooling to room temperature, the mixture was diluted with H_2O (5 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex Kinetex C_{18} column, 0–40% MeCN:H_2O with 0.1% formic acid modifier) to give 5-chloro-1'-{2-[(1-methyl-2-oxo-2,3-dihydro-1H-indol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 65**). ^{1}H NMR (500 MHz, CD_3CN): δ 8.34 (s, 1H), 7.36 (d, J = 2.2 Hz, 1H), 7.12 (dd, J = 8.3, 2.1 Hz, 1H), 6.87–6.83 (m, 1H), 6.82–6.75 (m, 2H), 6.70 (d, J = 8.5 Hz, 1H), 4.04 (t, J = 5.6 Hz, 2H), 3.34 (s, 2H), 3.02 (s, 3H), 3.00–2.91 (m, 2H), 2.85 (t, J = 5.6 Hz, 2H), 2.78–2.70 (m, 2H), 1.82–1.70 (m, 4H). MS = 426.1 $[M+H]^+$.

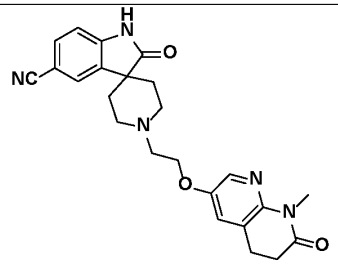
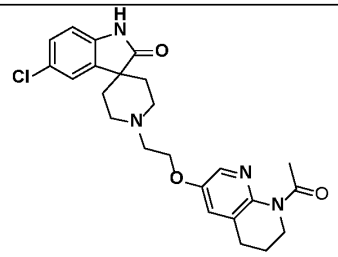
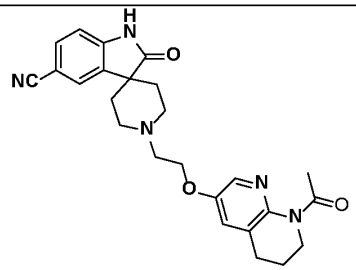
[1088] The following compound in Table 28 was prepared according to procedures analogous to those described for **Compound 65** using the appropriate starting materials.

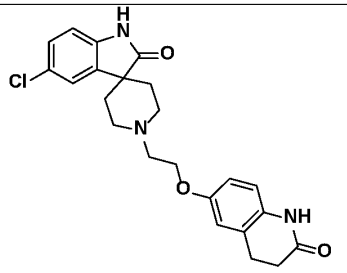
Table 28.

#	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Inter-mediates Used
66		1'-[2-(4-methanesulfonylphenoxy)ethyl]-5-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 415.2 Found 415.1	**A-3**
67		1'-[2-(4-methanesulfonylphenoxy)ethyl]-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 415.2 Found 415.1	**A-3** and **B-6**
68		5-chloro-1'-{2-[(1-methyl-1H-indazol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 411.2 Found 411.1	**A-5** and **B-4**
69		5-chloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 435.1 Found 435.0	**A-3** and **B-4**

70		1'-{2-[(1-methyl-1H-indazol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 377.2 Found 377.1	**A-5**
71		1'-[2-(4-methanesulfonylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 426.1 Found 426.1	**A-3** and **B-9**
72		5-bromo-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 479.1 Found 479.1	**A-3**
73		1'-[2-(4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 401.2 Found 401.2	**A-3**
74		1'-[2-(3-fluoro-4-methanesulfonylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 444.1 Found 444.1	**A-6** and **B-9**

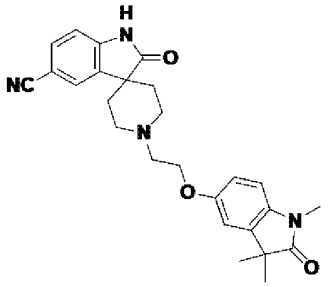
75		*N*-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-*N*-methylmethanesulfonamide	Calc'd 455.2 Found 455.2	**A-7** and **B-9**
76		N-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-N-methylmethanesulfonamide	Calc'd 464.1 Found 464.2	**A-7** and **B-4**
77		1'-[2-(4-{[dimethyl(oxo)-λ⁶-sulfanylidene]amino}phenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 439.2 Found 439.2	**A-8** and **B-9**
78		5-chloro-1'-{2-[(8-methyl-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 441.2 Found 441.1	**A-72** and **B-4**

79		1'-{2-[(8-methyl-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 432.2 Found 432.2	**A-72** and **B-9**
80		1'-{2-[(8-acetyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 455.2 Found 455.1	**A-73** and **B-4**
81		1'-{2-[(8-acetyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 446.2 Found 446.2	**A-73** and **B-9**

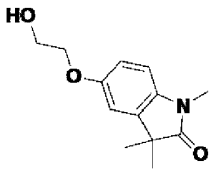
82		5-chloro-1'-{2-[(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 426.2 Found 426.2	**A-83** and **B-4**

Example 24

2-oxo-1'-{2-[(1,3,3-trimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (Compound 83)

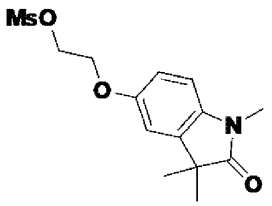


Step 1: 5-(2-hydroxyethoxy)-1,3,3-trimethyl-2,3-dihydro-1H-indol-2-one



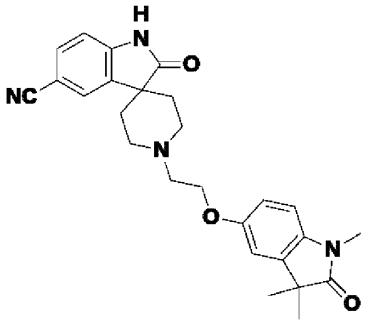
[1089] A mixture of 5-hydroxy-1,3,3-trimethyl-2,3-dihydro-1H-indol-2-one (100 mg, 0.523 mmol), ethylene carbonate (69.7 µL, 1.05 mmol) and K_2CO_3 (0.145 g, 1.05 mmol) in DMF (5 mL) was heated at 90 °C for 3 h. After cooling to room temperature, the mixture was diluted with H_2O (10 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 10 g cartridge, 0–100% EtOAc:hexanes) to give 5-(2-hydroxyethoxy)-1,3,3-trimethyl-2,3-dihydro-1H-indol-2-one. MS = 236.1 $[M+H]^+$.

Step 2: 2-[(1,3,3-trimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)oxy]ethyl methanesulfonate



[1090] To a solution of 5-(2-hydroxyethoxy)-1,3,3-trimethyl-2,3-dihydro-1H-indol-2-one (65.0 mg, 0.276 mmol) and TEA (57.9 µL, 0.414 mmol) in DCM (2 mL) was added methanesulfonyl chloride (25.6 µL, 0.332 mmol). The mixture was stirred for 30 min, then quenched with H_2O (5 mL) and extracted with DCM (2 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo and used in the subsequent step without further purification. MS = 314.1 $[M+H]^+$.

Step 3: 2-oxo-1'-{2-[(1,3,3-trimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (Compound 83)

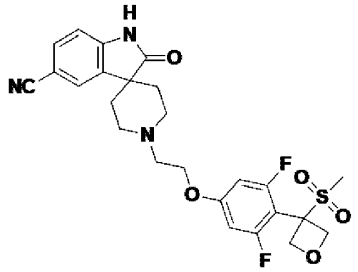


[1091] A mixture of 2-[(1,3,3-trimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)oxy]ethyl methanesulfonate (84.0 mg, 0.268 mmol), 2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (**Intermediate B-9**, 64.0 mg, 0.241 mmol, HCl salt) and K_2CO_3 (93.0 mg, 0.670 mmol) in DMF (1.2 mL) was heated at 60 °C for 3 h. After cooling to room temperature, the mixture was diluted with H_2O (10 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex Kinetex C_{18} column, 0–30% MeCN:H_2O with 0.1% formic acid modifier) to give 2-oxo-1'-{2-[(1,3,3-trimethyl-2-oxoindol-5-yl)oxy]ethyl}-1H-spiro[indole-3,4'-piperidine]-5-carbonitrile (**Compound 83**). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.87 (s, 1H), 7.96 (s, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.09 (d, J = 2.5 Hz, 1H), 7.00 (d, J = 8.1 Hz,

1H), 6.94–6.84 (m, 2H), 4.11 (t, J = 5.8 Hz, 2H), 3.10 (s, 3H), 2.96–2.83 (m, 4H), 2.81–2.70 (m, 2H), 1.85–1.71 (m, 4H), 1.26 (s, 6H). MS = 445.2 $[M+H]^+$.

Example 25

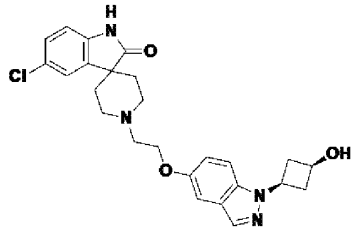
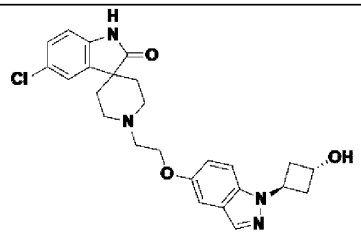
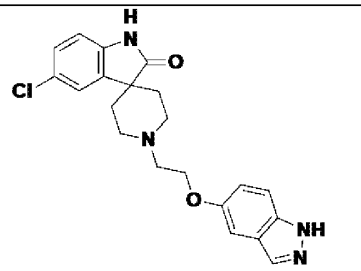
1'-{2-[3,5-difluoro-4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (Compound 84)

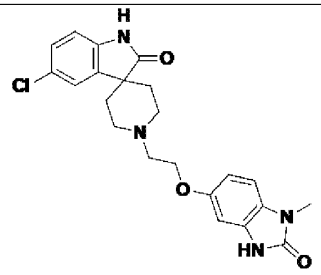
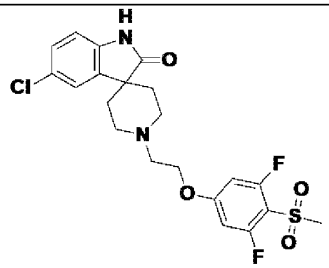
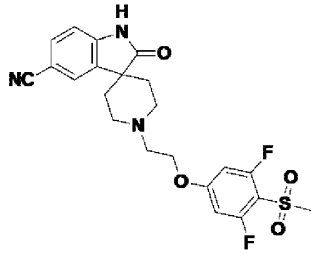
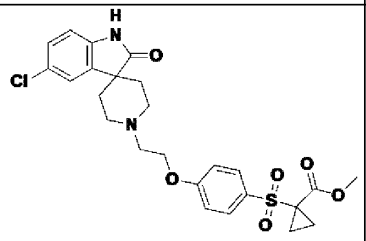


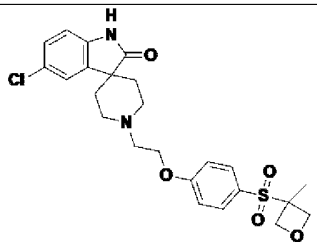
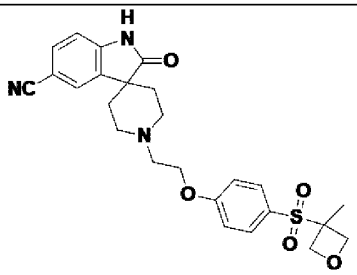
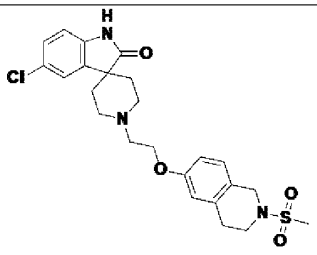
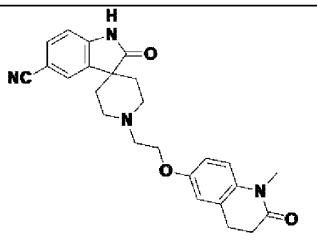
[1092] To a solution of 3-[4-(2-bromoethoxy)-2,6-difluorophenyl]-3-methanesulfonyloxetane (**Intermediate A-32**, 60.0 mg, 0.162 mmol) in MeCN (1.00 mL) was added $NaHCO_3$ (40.7 mg, 0.485 mmol) and 2-oxospiro[indoline-3,4'-piperidine]-5-carbonitrile (**Intermediate B-9**, 46.89 mg, 177.8 µmol, HCl salt). The mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was filtered and washed with MeCN. The filtrate was concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters Xbridge BEH C_{18} column, 25–55% MeCN:H_2O with 10 mM NH_4HCO_3 modifier) to give 1'-{2-[3,5-difluoro-4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (**Compound 84**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.86 (s, 1H), 7.96 (s, 1H), 7.67 (d, J = 8.4 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 10.8 Hz, 2H), 5.14 (dd, J = 14.4, 8.0 Hz, 4H), 4.21 (t, J = 5.2 Hz, 2H), 3.13 (s, 3H), 2.89–2.85 (m, 4H), 2.74–2.71 (m, 2H), 1.81–1.72 (m, 4H). MS = 518.2 $[M+H]^+$.

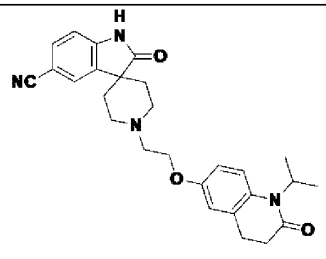
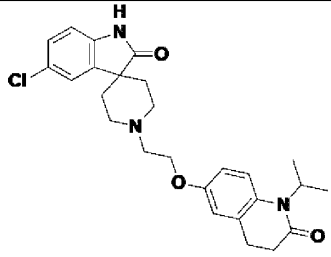
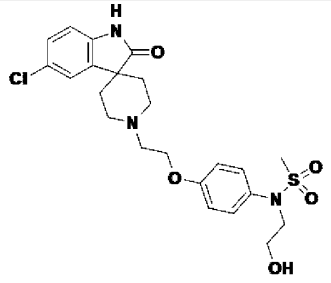
[1093] The following compounds in Table 29 were prepared according to procedures analogous to those described for **Compound 84** using the appropriate starting materials. In cases where step 1 was followed by chiral SFC purification to separate isomers, chiral column conditions and elution order are specified.

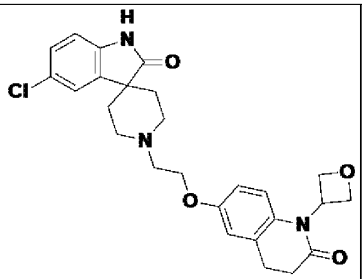
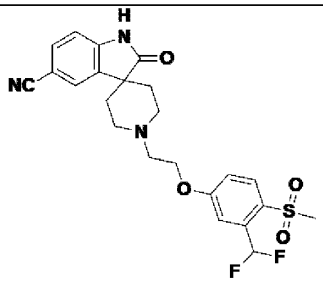
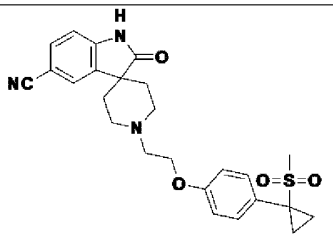
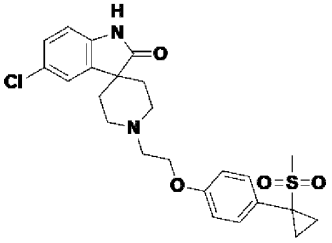
Table 29.

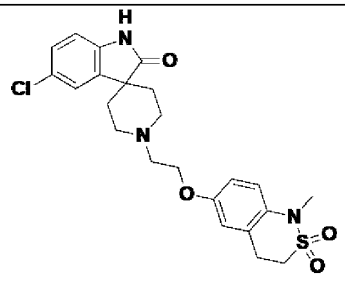
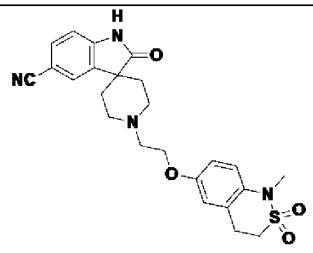
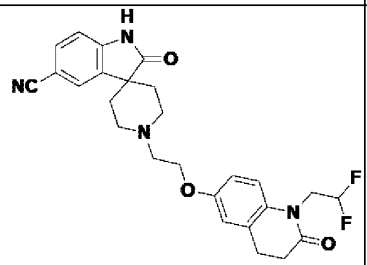
#	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Inter-mediates Used	Chiral Column, If Applicable	Elution Order
85		5-chloro-1'-[2-({1-[(*cis*)-3-hydroxycyclobutyl]-1H-indazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 467.2 Found 467.3	**A-63** and **B-4**	n/a	n/a
86		5-chloro-1'-[2-({1-[(*trans*)-3-hydroxycyclobutyl]-1H-indazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 467.2 Found 467.3	**A-62** and **B-4**	n/a	n/a
87		5-chloro-1'-[2-(2H-indazol-5-yloxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 397.1 Found 397.1	**A-80** and **B-4**	n/a	n/a

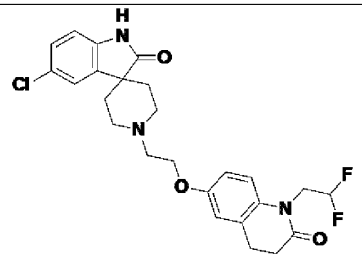
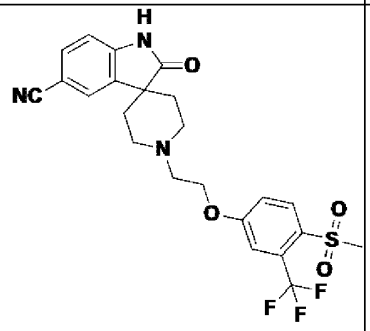
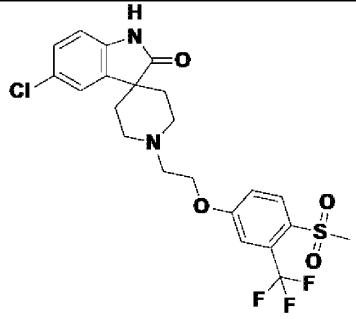
88		5-chloro-1'-{2-[(1-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 427.1 Found 427.2	**A-82** and **B-4**	n/a	n/a
89		5-chloro-1'-[2-(3,5-difluoro-4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 471.1 Found 471.1	**A-18** and **B-4**	n/a	n/a
90		1'-[2-(3,5-difluoro-4-methanesulfonylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 462.1 Found 462.0	**A-18** and **B-9**	n/a	n/a
91		methyl 1-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzenesulfonyl]cyclopropane-1-carboxylate	Calc'd 519.1 Found 519.1	**A-24** and **B-4**	n/a	n/a

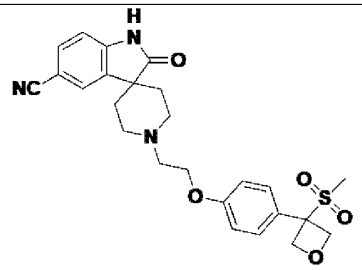
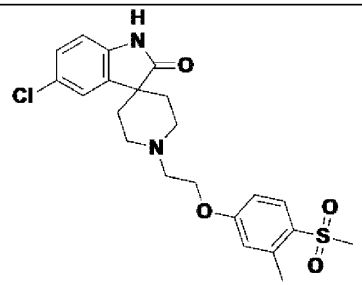
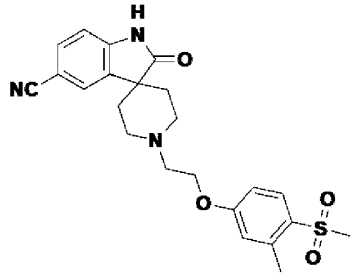
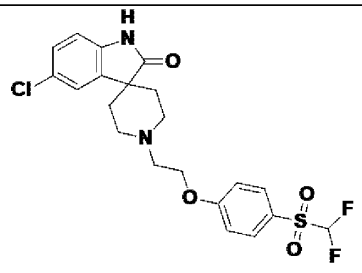
92		5-chloro-1'-(2-{4-[(3-methyloxetan-3-yl)sulfonyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 491.1 Found 491.2	**A-27** and **B-4**	n/a	n/a
93		1'-(2-{4-[(3-methyloxetan-3-yl)sulfonyl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 482.2 Found 482.2	**A-27** and **B-9**	n/a	n/a
94		5-chloro-1'-{2-[(2-methanesulfonyl-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 490.1 Found 490.2	**A-55** and **B-4**	n/a	n/a
95		1'-{2-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indol	Calc'd 431.2 Found 431.3	**A-71** and **B-9**	n/a	n/a

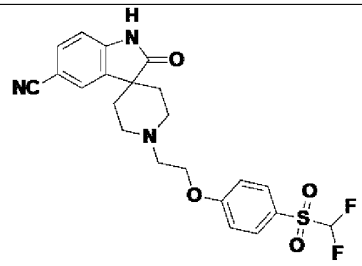
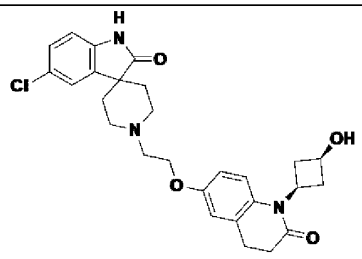
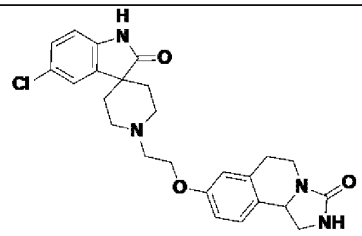
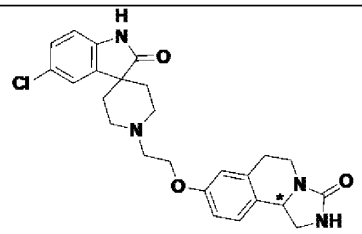
		e-3,4'-piperidine]-5-carbonitrile				
96		2-oxo-1'-(2-{[2-oxo-1-(propan-2-yl)-1,2,3,4-tetrahydroquinolin-6-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 459.2 Found 459.1	**A-64** and **B-9**	n/a	n/a
97		5-chloro-1'-(2-{[2-oxo-1-(propan-2-yl)-1,2,3,4-tetrahydroquinolin-6-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 468.2 Found 468.2	**A-64** and **B-4**	n/a	n/a
98		*N*-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-*N*-(2-hydroxyethyl)methanesulfonamide	Calc'd 494.1 Found 494.1	**A-68** and **B-4**	n/a	n/a

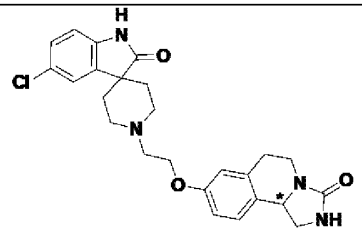
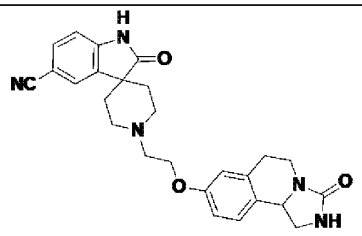
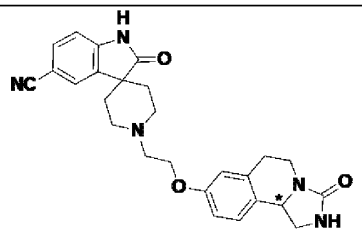
99		5-chloro-1'-(2-{[1-(oxetan-3-yl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 482.2 Found 482.2	**A-66** and **B-4**	n/a	n/a
100		1'-{2-[3-(difluoromethyl)-4-methanesulfonylphenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 476.1 Found 476.2	**A-13** and **B-9**	n/a	n/a
101		1'-{2-[4-(1-methanesulfonylcyclopropyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 466.2 Found 466.2	**A-28** and **B-9**	n/a	n/a
102		5-chloro-1'-{2-[4-(1-methanesulfonylcyclopropyl)phenoxy]ethyl}-1,2-dihydrospiro[indol	Calc'd 475.1 Found 475.2	**A-28** and **B-4**	n/a	n/a

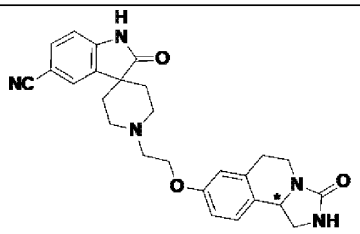
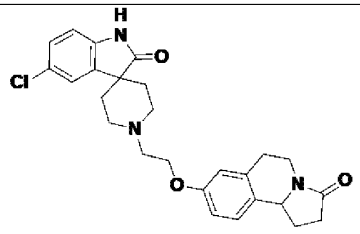
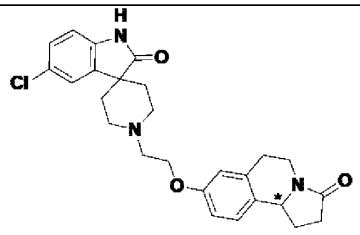
		e-3,4'-piperidin]-2-one				
103		6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-1-methyl-3,4-dihydro-1H-2λ⁶,1-benzothiazine-2,2-dione	Calc'd 476.1 Found 476.2	**A-51** and **B-4**	n/a	n/a
104		1'-{2-[(1-methyl-2,2-dioxo-3,4-dihydro-1H-2λ⁶,1-benzothiazin-6-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 467.2 Found 467.2	**A-51** and **B-9**	n/a	n/a
105		1'-(2-{[1-(2,2-difluoroethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 481.2 Found 481.3	**A-67** and **B-9**	n/a	n/a

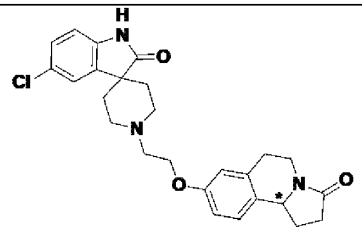
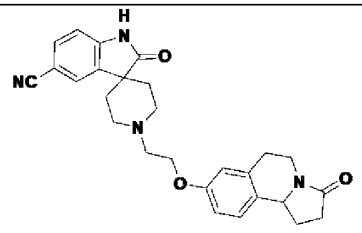
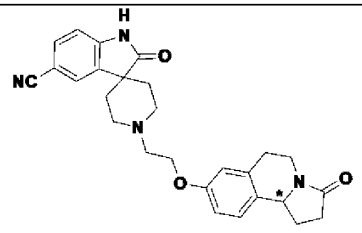
106		5-chloro-1'-(2-{[1-(2,2-difluoroethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 490.2 Found 490.3	**A-67** and **B-4**	n/a	n/a
107		1'-{2-[4-methanesulfonyl-3-(trifluoromethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 494.1 Found 494.1	**A-17** and **B-9**	n/a	n/a
108		5-chloro-1'-{2-[4-methanesulfonyl-3-(trifluoromethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 503.1 Found 503.1	**A-17** and **B-4**	n/a	n/a

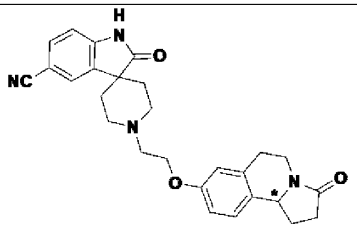
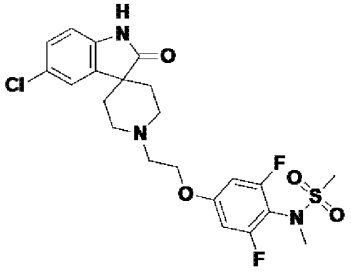
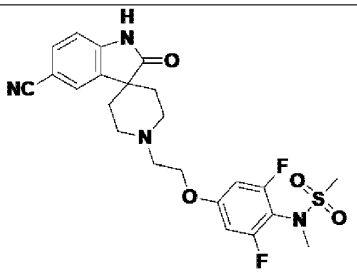
109		1'-{2-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 482.2 Found 482.1	**A-33** and **B-9**	n/a	n/a
110		5-chloro-1'-[2-(4-methanesulfonyl-3-methylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 449.1 Found 449.1	**A-22** and **B-4**	n/a	n/a
111		1'-[2-(4-methanesulfonyl-3-methylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 440.2 Found 440.2	**A-22** and **B-9**	n/a	n/a
112		5-chloro-1'-[2-(4-difluoromethanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 471.1 Found 471.1	**A-16** and **B-4**	n/a	n/a

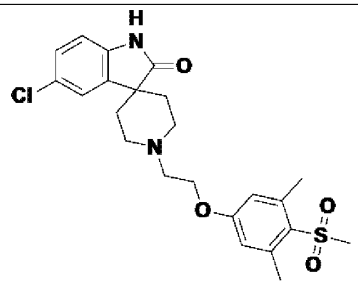
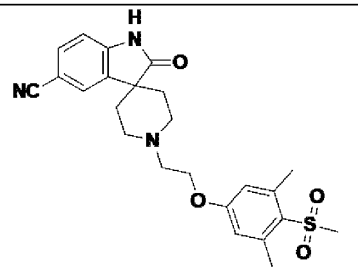
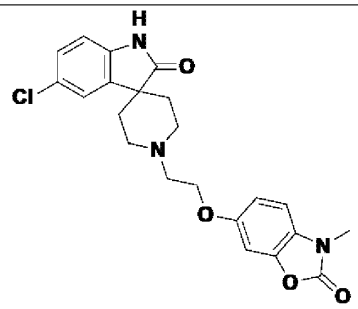
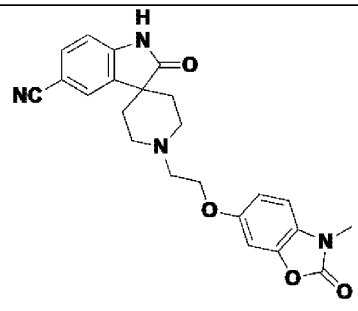
113		1'-[2-(4-difluoromethanesulfonylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 462.1 Found 462.2	**A-16** and **B-9**	n/a	n/a
114		5-chloro-1'-[2-({2-oxo-1-[(*cis)*-3-hydroxycyclobutyl]-1,2,3,4-tetrahydroquinolin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 496.2 Found 496.2	**A-69** and **B-4**	n/a	n/a
115		5-chloro-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 467.2 Found 467.2	**A-58** and **B-4**	n/a	n/a
116		*(S)* or *(R)*-5-chloro-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-	Calc'd 467.2 Found 467.2	**A-58** and **B-4**	Daicel Chiralpak AD-3	Second

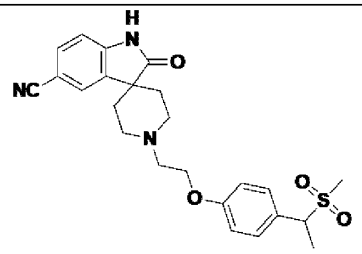
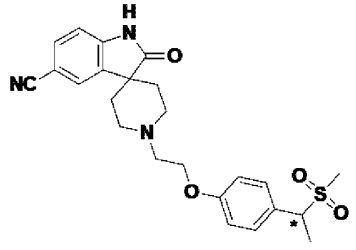
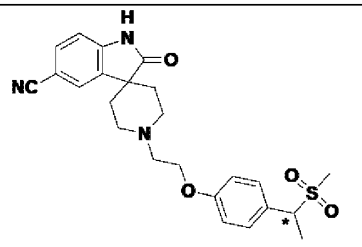
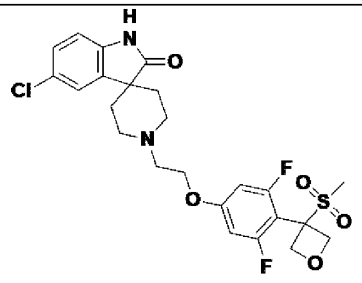
		imidazo[4,3-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one				
117		*(R)* or (*S*)-5-chloro-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 467.2 Found 467.2	**A-58** and **B-4**	Daicel Chiralpak AD-3	First
118		2-oxo-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 458.2 Found 458.3	**A-58** and **B-9**	n/a	n/a
119		*(S)* or (*R*)-2-oxo-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-imidazo[4,3-	Calc'd 458.2 Found 458.3	**A-58** and **B-9**	Daicel Chiralpak AD-3	First

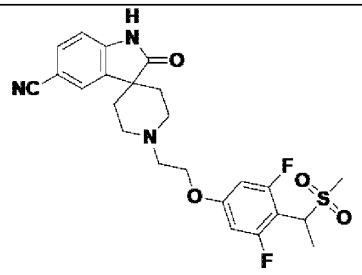
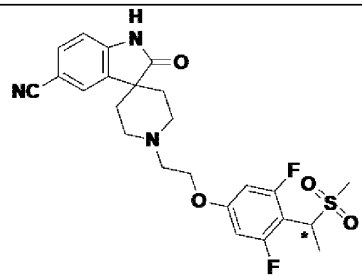
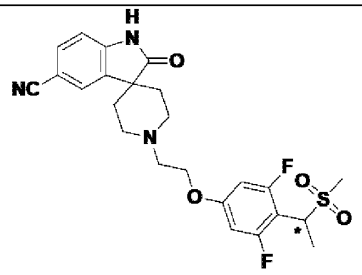
		a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile				
120		*(R)* or (*S*)-2-oxo-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-imidazo[4,3-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 458.2 Found 458.3	**A-58** and **B-9**	Daicel Chiralpak AD-3	Second
121		5-chloro-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 466.2 Found 466.1	**A-57** and **B-4**	n/a	n/a
122		*(S)* or (*R*)-5-chloro-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indol	Calc'd 466.2 Found 466.1	**A-57** and **B-4**	Daicel Chiralpak AD-3	First

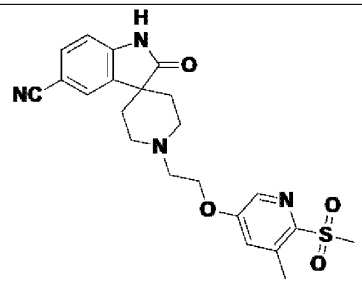
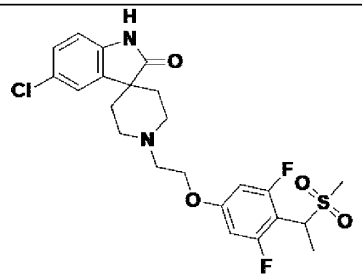
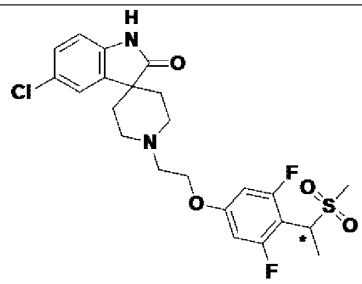
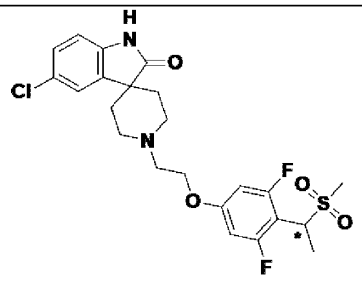
		e-3,4'-piperidin]-2-one				
123		*(R)* or (*S*)-5-chloro-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 466.2 Found 466.1	**A-57** and **B-4**	Daicel Chiralpak AD-3	Second
124		2-oxo-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 457.2 Found 457.1	**A-57** and **B-9**	n/a	n/a
125		*(S)* or (*R*)-2-oxo-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 457.2 Found 457.1	**A-57** and **B-9**	Daicel Chiralpak AD-3	n/a

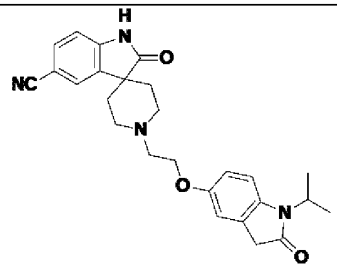
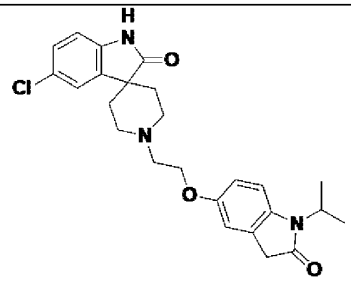
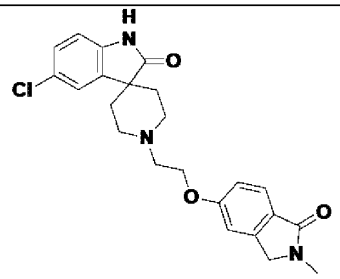
126		*(R)* or (*S*)-2-oxo-1'-[2-({3-oxo-1H,2H,3H,5H,6H,10bH-pyrrolo[2,1-a]isoquinolin-8-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 457.2 Found 457.1	**A-57** and **B-9**	Daicel Chiralpak AD-3	n/a
127		*N*-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,6-difluorophenyl]-*N*-methylmethanesulfonamide	Calc'd 500.1 Found 500.2	**A-44** and **B-4**	n/a	n/a
128		*N*-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,6-difluorophenyl]-*N*-methylmethanesulfonamide	Calc'd 491.1 Found 491.2	**A-44** and **B-9**	n/a	n/a

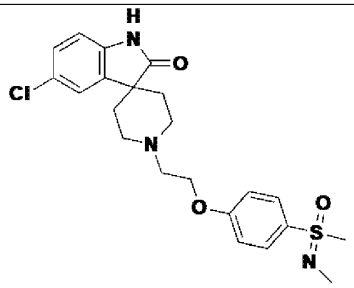
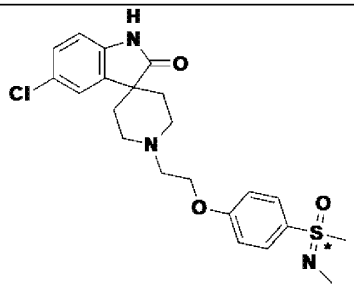
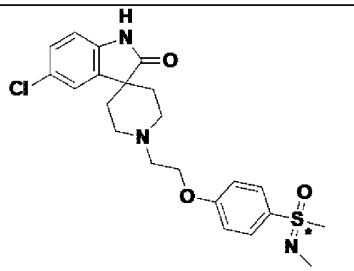
129		5-chloro-1'-[2-(4-methanesulfonyl-3,5-dimethylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 463.1 Found 463.1	**A-20** and **B-4**	n/a	n/a
130		1'-[2-(4-methanesulfonyl-3,5-dimethylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 454.2 Found 454.2	**A-20** and **B-9**	n/a	n/a
131		5-chloro-1'-{2-[(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 428.1 Found 428.1	**A-59** and **B-4**	n/a	n/a
132		1'-{2-[(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indol	Calc'd 419.2 Found 419.2	**A-59** and **B-9**	n/a	n/a

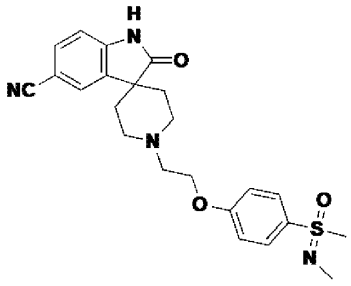
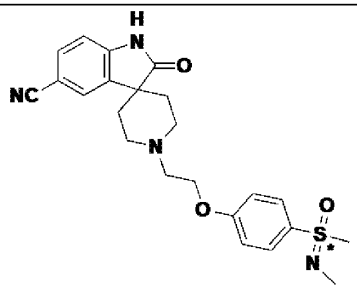
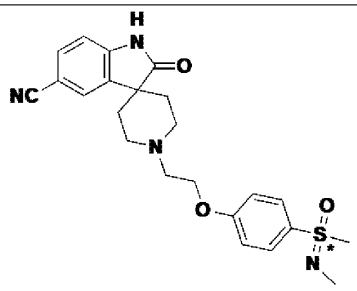
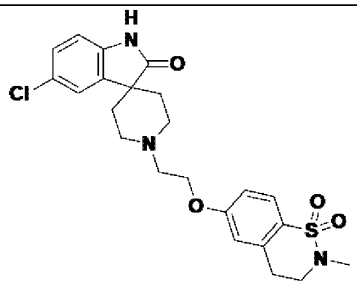
		e-3,4'-piperidine]-5-carbonitrile				
133		1'-{2-[4-(1-methanesulfonylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 454.2 Found 454.2	**A-31** and **B-9**	n/a	n/a
134		*(S)* or *(R)*-1'-{2-[4-(1-methanesulfonylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 454.2 Found 454.2	**A-31** and **B-9**	Daicel Chiralpak OD-3	First
135		*(R)* or *(S)*-1'-{2-[4-(1-methanesulfonylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 454.2 Found 454.2	**A-31** and **B-9**	Daicel Chiralpak OD-3	Second
136		5-chloro-1'-{2-[3,5-difluoro-4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-1,2-dihydrospiro[indol	Calc'd 527.1 Found 527.2	**A-32** and **B-4**	n/a	n/a

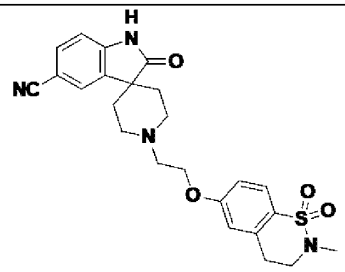
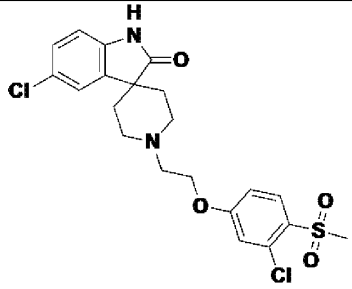
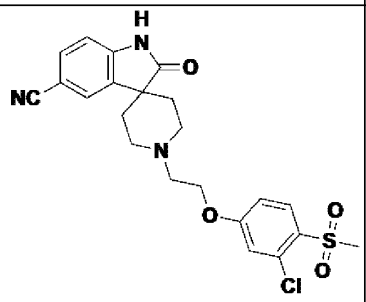
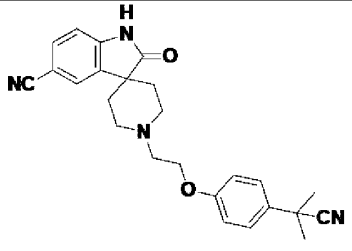
		e-3,4'-piperidin]-2-one				
137		1'-{2-[3,5-difluoro-4-(1-methanesulfonylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 490.2 Found 490.2	**A-30** and **B-9**	n/a	n/a
138		*(S)* or (*R*)-1'-{2-[3,5-difluoro-4-(1-methanesulfonylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 490.2 Found 490.2	**A-30** and **B-9**	Daicel Chiralpak OD-3	First
139		*(R)* or (*S*)-1'-{2-[3,5-difluoro-4-(1-methanesulfonylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 490.2 Found 490.2	**A-30** and **B-9**	Daicel Chiralpak OD-3	Second

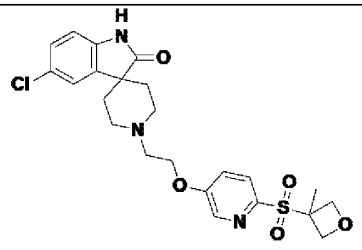
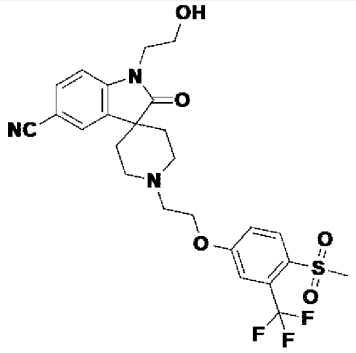
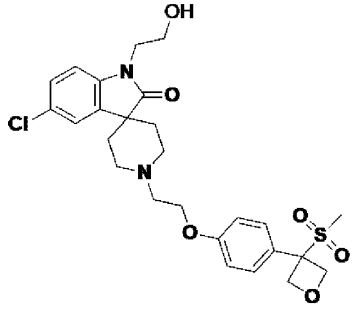
140		1'-{2-[(6-methanesulfonyl-5-methylpyridin-3-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 441.2 Found 441.1	**A-21** and **B-9**	n/a	n/a
141		5-chloro-1'-{2-[3,5-difluoro-4-(1-methanesulfonylethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 499.1 Found 499.2	**A-30** and **B-4**	n/a	n/a
142		*(S)* or *(R)*-5-chloro-1'-{2-[3,5-difluoro-4-(1-methanesulfonylethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 499.1 Found 499.2	**A-30** and **B-4**	Daicel Chiralpak OD-3	First
143		*(R)* or *(S)*-5-chloro-1'-{2-[3,5-difluoro-4-(1-methanesulfonylethyl)phenoxy]ethyl}-1,2-dihydrospiro[indol	Calc'd 499.1 Found 499.2	**A-30** and **B-4**	Daicel Chiralpak OD-3	Second

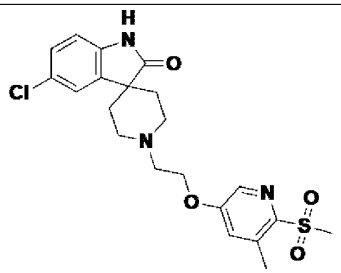
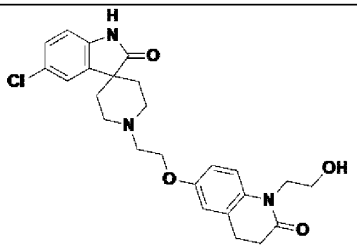
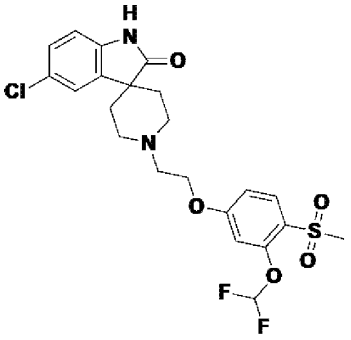
		e-3,4'-piperidin]-2-one				
144		2-oxo-1'-(2-{[2-oxo-1-(propan-2-yl)-2,3-dihydro-1H-indol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 445.2 Found 445.3	**A-14** and **B-9**	n/a	n/a
145		5-chloro-1'-(2-{[2-oxo-1-(propan-2-yl)-2,3-dihydro-1H-indol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 454.2 Found 454.2	**A-14** and **B-4**	n/a	n/a
146		5-chloro-1'-{2-[(2-methyl-1-oxo-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 426.2 Found 426.1	**A-53** and **B-4**	n/a	n/a

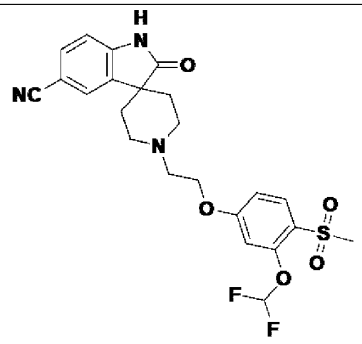
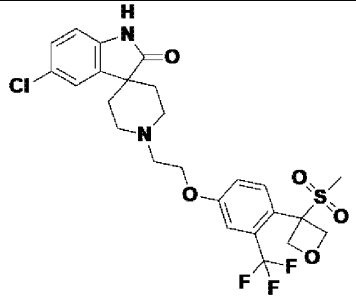
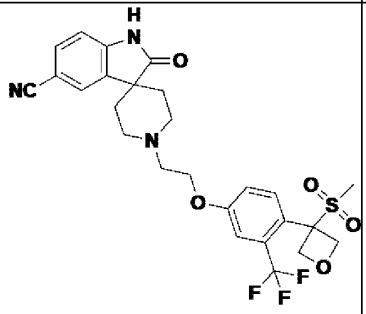
147		5-chloro-1'-(2-{4-[methyl(methylimino)oxo-λ⁶-sulfanyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 448.1 Found 448.0	**A-45** and **B-4**	n/a	n/a
148		*(S)* or *(R)*-5-chloro-1'-(2-{4-[methyl(methylimino)oxo-λ⁶-sulfanyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 448.1 Found 448.0	**A-45** and **B-4**	Daicel Chiralpak ID-3	First
149		*(R)* or *(S)*-5-chloro-1'-(2-{4-[methyl(methylimino)oxo-λ⁶-sulfanyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 448.1 Found 448.0	**A-45** and **B-4**	Daicel Chiralpak ID-3	Second

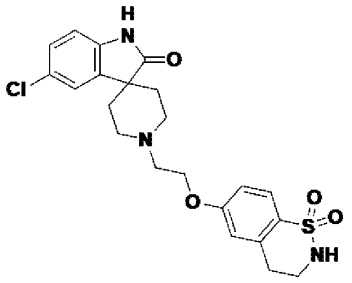
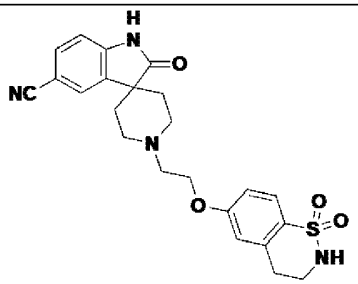
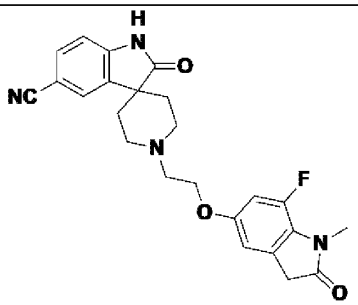
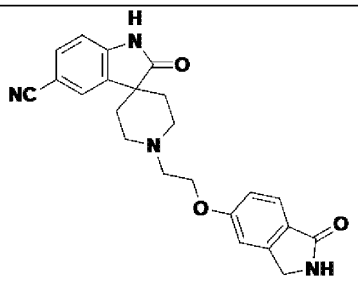
150		1'-(2-{4-[methyl(methylimino)oxo-λ⁶-sulfanyl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 439.2 Found 439.0	**A-45** and **B-9**	n/a	n/a
151		*(S)* or (*R*)-1'-(2-{4-[methyl(methylimino)oxo-λ⁶-sulfanyl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 439.2 Found 439.0	**A-45** and **B-9**	Daicel Chiralpak ID-3	Second
152		*(R)* or (*S*)-1'-(2-{4-[methyl(methylimino)oxo-λ⁶-sulfanyl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 439.2 Found 439.0	**A-45** and **B-9**	Daicel Chiralpak ID-3	First
153		6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-methyl-3,4-dihydro-2H-1λ⁶,2-	Calc'd 476.1 Found 476.1	**A-49** and **B-4**	n/a	n/a

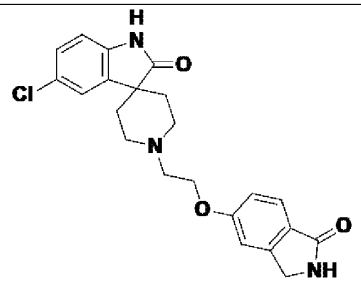
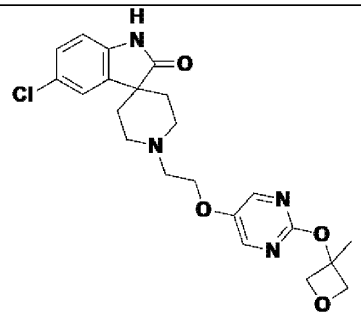
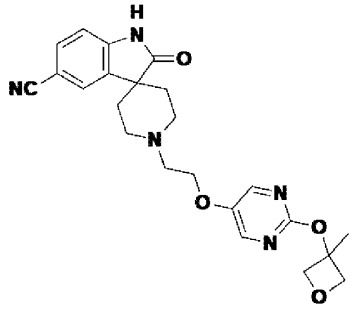
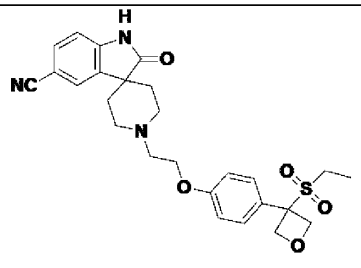
		benzothiazine-1,1-dione				
154		1'-{2-[(2-methyl-1,1-dioxo-3,4-dihydro-2H-1λ⁶,2-benzothiazin-6-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 467.2 Found 467.2	**A-49** and **B-9**	n/a	n/a
155		5-chloro-1'-[2-(3-chloro-4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 469.1 Found 469.2	**A-19** and **B-4**	n/a	n/a
156		1'-[2-(3-chloro-4-methanesulfonylphenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 460.1 Found 460.2	**A-19** and **B-9**	n/a	n/a
157		1'-{2-[4-(1-cyano-1-methylethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indol	Calc'd 415.2 Found 415.2	**A-47** and **B-9**	n/a	n/a

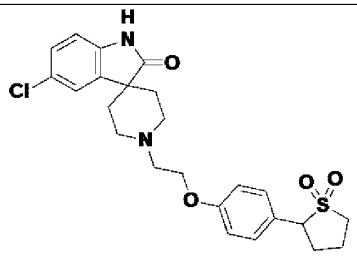
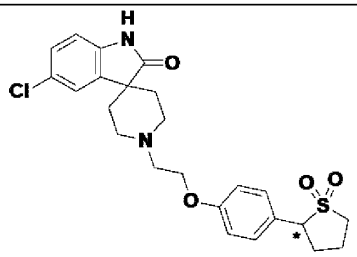
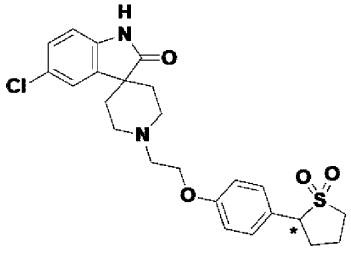
		e-3,4'-piperidine]-5-carbonitrile				
158		5-chloro-1'-[2-({6-[(3-methyloxetan-3-yl)sulfonyl]pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 492.1 Found 492.1	**A-26** and **B-4**	n/a	n/a
159		1-(2-hydroxyethyl)-1'-{2-[4-methanesulfonyl-3-(trifluoromethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 538.2 Found 538.2	**A-17** and **B-12**	n/a	n/a
160		5-chloro-1-(2-hydroxyethyl)-1'-{2-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 535.2 Found 535.2	**A-33** and **B-11**	n/a	n/a

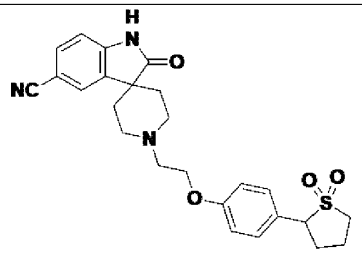
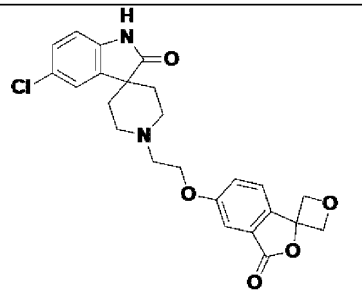
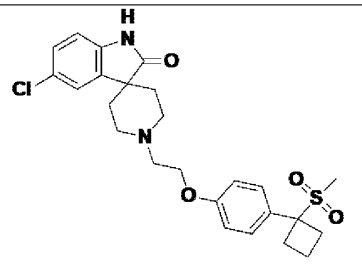
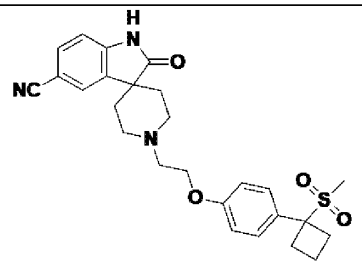
161		5-chloro-1'-{2-[(6-methanesulfonyl-5-methylpyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 450.1 Found 450.1	**A-21** and **B-4**	n/a	n/a
162		5-chloro-1'-(2-{[1-(2-hydroxyethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 470.2 Found 470.1	**A-65** and **B-4**	n/a	n/a
163		5-chloro-1'-{2-[3-(difluoromethoxy)-4-methanesulfonylphenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 501.1 Found 501.2	**A-23** and **B-4**	n/a	n/a

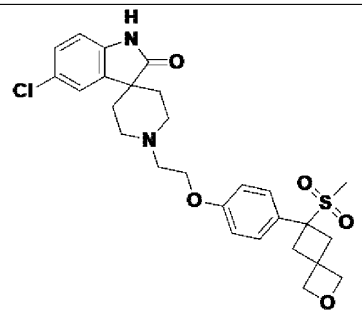
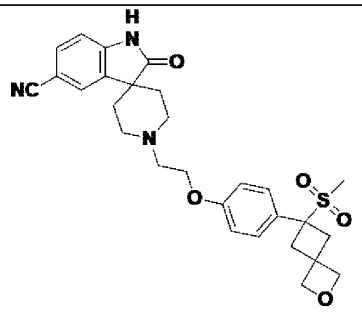
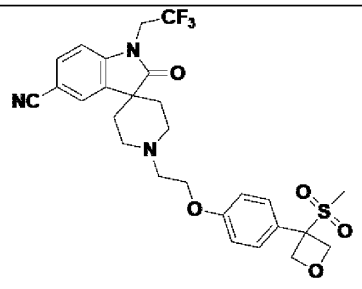
164		1'-{2-[3-(difluoromethoxy)-4-methanesulfonylphenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 492.1 Found 492.2	**A-23** and **B-9**	n/a	n/a
165		5-chloro-1'-{2-[4-(3-methanesulfonyloxetan-3-yl)-3-(trifluoromethyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 559.1 Found 559.2	**A-34** and **B-4**	n/a	n/a
166		1'-{2-[4-(3-methanesulfonyloxetan-3-yl)-3-(trifluoromethyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 550.2 Found 550.2	**A-34** and **B-9**	n/a	n/a

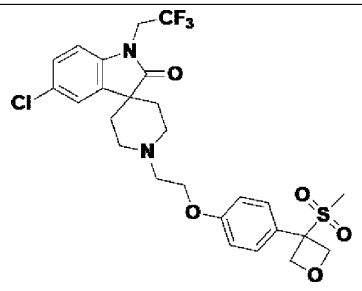
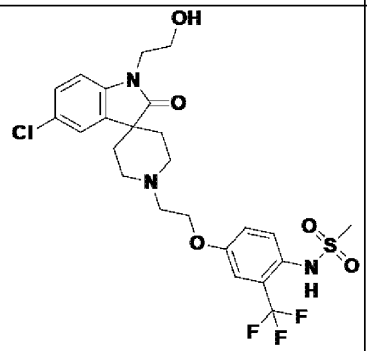
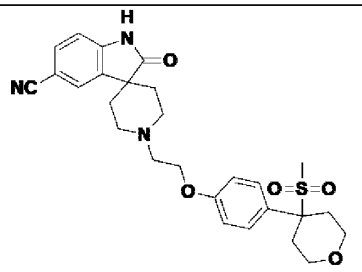
167		6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-3,4-dihydro-2H-1λ⁶,2-benzothiazine-1,1-dione	Calc'd 462.1 Found 462.0	**A-50** and **B-4**	n/a	n/a
168		1'-{2-[(1,1-dioxo-3,4-dihydro-2H-1λ⁶,2-benzothiazin-6-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 453.2 Found 453.2	**A-50** and **B-9**	n/a	n/a
169		1'-{2-[(7-fluoro-1-methyl-2-oxo-2,3-dihydro-1H-indol-5-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 435.2 Found 435.1	**A-60** and **B-9**	n/a	n/a
170		2-oxo-1'-{2-[(1-oxo-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 403.2 Found 403.3	**A-61** and **B-9**	n/a	n/a

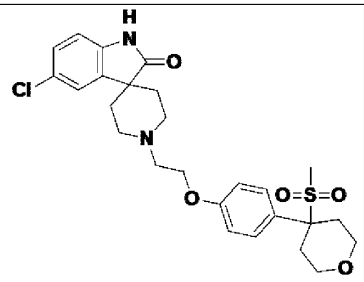
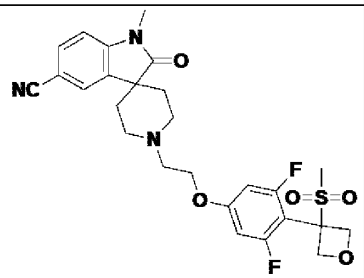
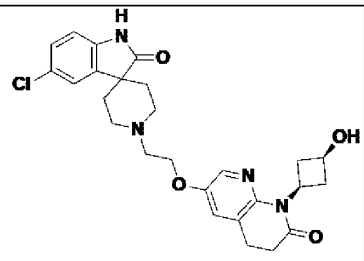
171		5-chloro-1'-{2-[(1-oxo-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 412.1 Found 412.2	**A-61** and **B-4**	n/a	n/a
172		5-chloro-1'-[2-({2-[(3-methyloxetan-3-yl)oxy]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 445.2 Found 445.2	**A-43** and **B-4**	n/a	n/a
173		1'-[2-({2-[(3-methyloxetan-3-yl)oxy]pyrimidin-5-yl}oxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 436.2 Found 436.2	**A-43** and **B-9**	n/a	n/a
174		1'-(2-{4-[3-(ethanesulfonyl)oxetan-3-yl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 496.2 Found 496.0	**A-37** and **B-9**	n/a	n/a

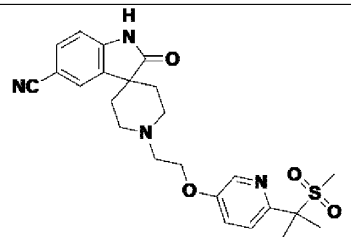
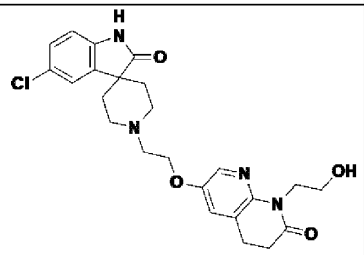
175		2-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-1λ⁶-thiolane-1,1-dione	Calc'd 475.1 Found 475.2	**A-38** and **B-4**	n/a	n/a
176		*(S)* or (*R*)-2-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-1λ⁶-thiolane-1,1-dione	Calc'd 475.1 Found 475.2	**A-38** and **B-4**	Regis(*S*, *S*)Whelk-O1	First
177		*(R)* or (*S*)-2-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-1λ⁶-thiolane-1,1-dione	Calc'd 475.1 Found 475.2	**A-38** and **B-4**	Regis(*S*, *S*)Whelk-O1	Second

178		1'-{2-[4-(1,1-dioxo-1λ⁶-thiolan-2-yl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 466.2 Found 466.2	**A-38** and **B-9**	n/a	n/a
179		5-chloro-1'-(2-{3-oxo-3H-spiro[2-benzofuran-1,3'-oxetan]-5-yloxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 455.1 Found 455.0	**A-38** and **B-9**	n/a	n/a
180		5-chloro-1'-{2-[4-(1-methanesulfonylcyclobutyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 489.2 Found 489.1	**A-40** and **B-4**	n/a	n/a
181		1'-{2-[4-(1-methanesulfonylcyclobutyl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 480.2 Found 480.2	**A-40** and **B-9**	n/a	n/a

182		5-chloro-1'-[2-(4-{6-methanesulfonyl-2-oxaspiro[3.3]heptan-6-yl}phenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 531.2 Found 531.1	**A-42** and **B-4**	n/a	n/a
183		1'-[2-(4-{6-methanesulfonyl-2-oxaspiro[3.3]heptan-6-yl}phenoxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 522.2 Found 522.1	**A-42** and **B-9**	n/a	n/a
184		1'-{2-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-2-oxo-1-(2,2,2-trifluoroethyl)-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 564.2 Found 564.2	**A-33** and **B-13**	n/a	n/a

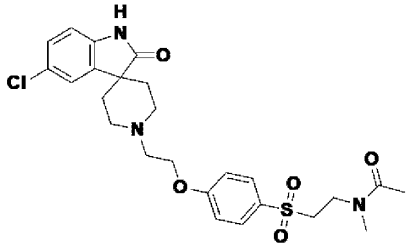
185		5-chloro-1'-{2-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-1-(2,2,2-trifluoroethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 573.1 Found 573.2	**A-33** and **B-14**	n/a	n/a
186		*N*-(4-{2-[5-chloro-1-(2-hydroxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl]ethoxy}-2-(trifluoromethyl)phenyl)methanesulfonamide	Calc'd 562.1 Found 562.1	**A-46** and **B-11**	n/a	n/a
187		1'-{2-[4-(4-methanesulfonyloxan-4-yl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 510.2 Found 510.2	**A-41** and **B-9**	n/a	n/a

188		5-chloro-1'-{2-[4-(4-methanesulfonyloxan-4-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 519.2 Found 519.2	**A-41** and **B-4**	n/a	n/a
189		1'-{2-[3,5-difluoro-4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 532.1 Found 532.2	**A-32** and **B-15**	n/a	n/a
190		5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 497.2 Found 497.2	**A-79** and **B-4**	n/a	n/a

191		1'-(2-{[6-(2-methanesulfonylpropan-2-yl)pyridin-3-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 469.2 Found 469.2	**A-78** and **B-9**	n/a	n/a
192		5-chloro-1'-(2-{[8-(2-hydroxyethyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 471.2 Found 471.2	**A-77** and **B-4**	n/a	n/a

Example 26

***N*-{2-[4-(2-{5-chloro-2-oxo-1,2-dihydrosiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzenesulfonyl]ethyl}-*N*-methylacetamide (Compound 193)**

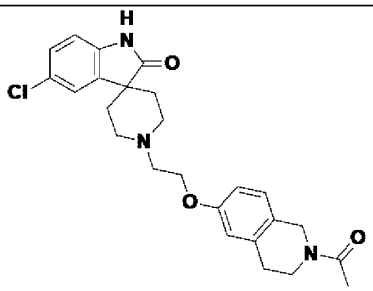
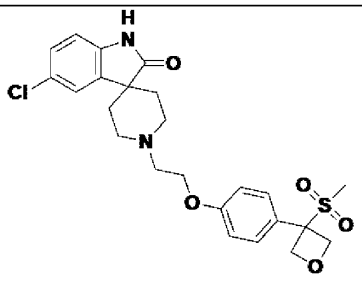


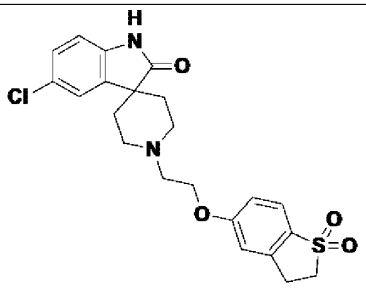
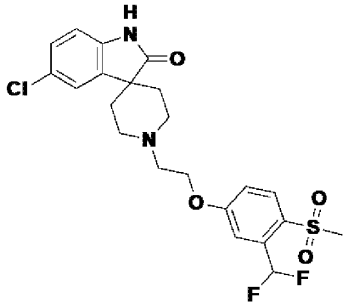
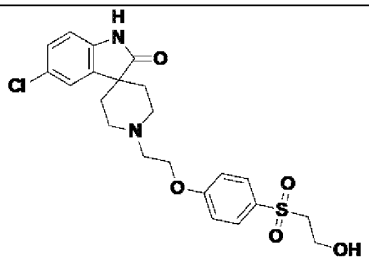
[1094] A mixture of 5-chloro-1'-(2-chloroethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-5**, 211 mg, 0.707 mmol), *N*-[2-(4-hydroxybenzenesulfonyl)ethyl]-*N*-methylacetamide (**Intermediate A-25**, 140 mg, 0.544 mmol) and K_2CO_3 (150 mg, 1.09 mmol) in DMF (4 mL) was stirred at 50 °C for 16 h. After cooling to room temperature, the mixture was filtered to remove solids. The filtrate was purified by reverse phase preparative HPLC (Phenomenex

Gemini-NX C_{18} column, 20–50% MeCN: 10 mM NH_4HCO_3 in H_2O) to give *N*-{2-[4-(2-{5-chloro-2-oxo-1,2-dihydrosiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzenesulfonyl]ethyl}-*N*-methylacetamide (**Compound 193**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 7.84–7.80 (m, 2H), 7.51 (s, 1H), 7.24–7.20 (m, 3H), 6.84 (d, J = 8.0, 1H), 4.26 (t, J = 5.6 Hz, 2H), 3.65–3.46 (m, 4H), 2.93–2.87 (m, 6H), 2.70–2.67 (m, 3H), 1.93 (s, 1H), 1.86 (s, 2H), 1.77–1.74 (m, 4H). MS = 520.2 $[M+H]^+$.

[1095] The following compounds in Table 30 were prepared according to procedures analogous to those described for **Compound 193** using the appropriate starting materials.

Table 30.

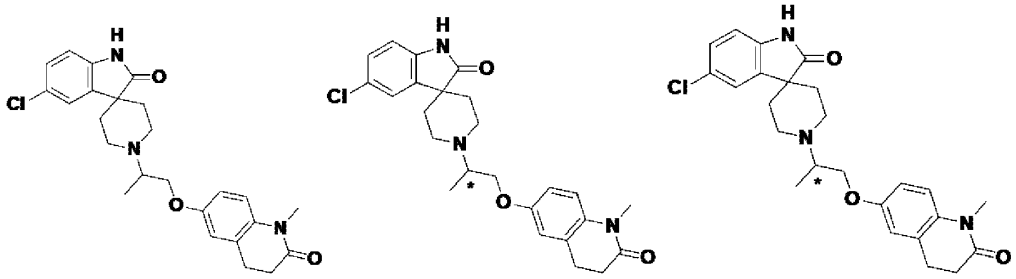
#	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Intermediates Used
194		1'-{2-[(2-acetyl-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy]ethyl}-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 454.2 Found 454.2	**A-56** and **B-5**
195		5-chloro-1'-{2-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 491.1 Found 491.1	**A-84** and **B-5**

196		5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,3-dihydro-1λ⁶-benzothiophene-1,1-dione	Calc'd 447.1 Found 447.2	**A-52** and **B-5**
197		5-chloro-1'-{2-[3-(difluoromethyl)-4-methanesulfonylphenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 485.1 Found 485.1	**A-12** and **B-5**
198		5-chloro-1'-{2-[4-(2-hydroxyethanesulfonyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 465.1 Found 465.1	**A-85** and **B-5**

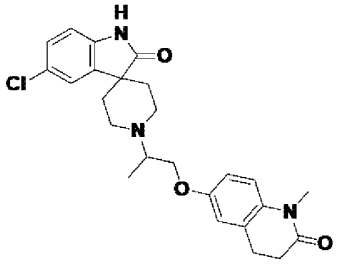
Example 27

5-chloro-1'-{1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 199), chloro-1'-[(2*S*) or (2*R*)-1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 200), and

chloro-1'-[(2*R*) or (2*S*)-1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 201)



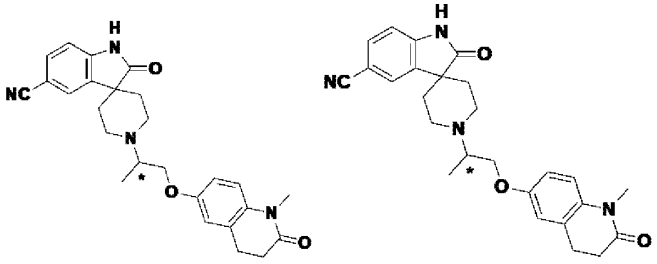
Step 1: 5-chloro-1'-{1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 199)



[1096] A solution of 1-methyl-6-(2-oxopropoxy)-1,2,3,4-tetrahydroquinolin-2-one (**Intermediate A-2**, 400 mg, 1.71 mmol), 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 406 mg, 1.71 mmol), Ti(i-PrO)$_4$ (506 µL, 1.71 mmol) and AcOH (9.81 µL, 0.171 mmol) in 1,2-dichloroethane (5 mL) was stirred at 50 °C for 2 h. The mixture was cooled to 0 °C and NaBH(OAc)$_3$ (545 mg, 2.57 mmol) was added in portionwise. The mixture was stirred at 50 °C for 12 hours. After cooling to 0 °C, the reaction mixture was quenched with H_2O (5 mL), and then filtered. The filtrate was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (8 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by reverse phase preparative HPLC (Waters Xbridge Prep OBD C_{18} column, 30–60% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-{1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 199**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 7.45 (s, 1H), 7.23 (d, J = 6.0 Hz, 1H), 7.01 (d, J = 8.8 Hz, 1H), 6.91–6.83 (m, 3H), 4.12–4.08 (m, 1H), 3.96–3.93 (m, 1H), 3.22

(s, 3H), 3.10–2.98 (m, 3H), 2.85–2.81 (m, 3H), 2.79–2.77 (m, 1H), 2.53–2.51 (m, 2H), 1.80–1.76 (m, 2H), 1.68–1.65 (m, 2H), 1.14 (d, J = 6.8 Hz, 3H). MS = 454.2 $[M+H]^+$.

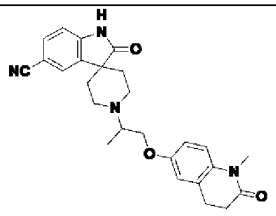
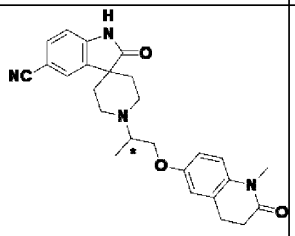
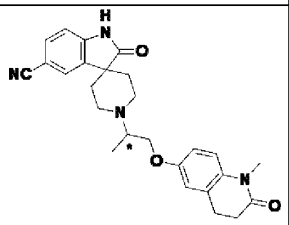
Step 2: chloro-1'-[(2*S*) or (2*R*)-1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 200) and chloro-1'-[(2*R*) or (2*S*)-1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 201)



[1097] 5-chloro-1'-{1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one was separated by preparative chiral SFC (Daicel Chiralpak AD-3, 42% ethanol with 0.1% NH_4OH in CO_2). The first eluting enantiomer of the title compound, chloro-1'-[(2*S*) or (2*R*)-1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 200**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 1H), 7.45 (s, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.01 (d, J = 8.8 Hz, 1H), 6.90–6.83 (m, 3H), 4.12–4.08 (m, 1H), 3.96–3.92 (m, 1H), 3.22 (s, 3H), 3.10–2.98 (m, 3H), 2.85–2.81 (m, 3H), 2.77–2.73 (m, 1H), 2.53–2.51 (m, 2H), 1.80–1.76 (m, 2H), 1.68–1.65 (m, 2H), 1.14 (d, J = 6.8 Hz, 3H). MS = 454.2 $[M+H]^+$. The second eluting enantiomer of the title compound, chloro-1'-[(2*R*) or (2*S*)-1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 201**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 1H), 7.45 (s, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 8.8 Hz, 1H), 6.91–6.83 (m, 3H), 4.12–4.08 (m, 1H), 3.95–3.93 (m, 1H), 3.22 (s, 3H), 3.10–2.98 (m, 3H), 2.85–2.81 (m, 3H), 2.77–2.73 (m, 1H), 2.53–2.51 (m, 2H), 1.78–1.76 (m, 2H), 1.68–1.65 (m, 2H), 1.14 (d, J = 6.8 Hz, 3H). MS = 454.2 $[M+H]^+$.

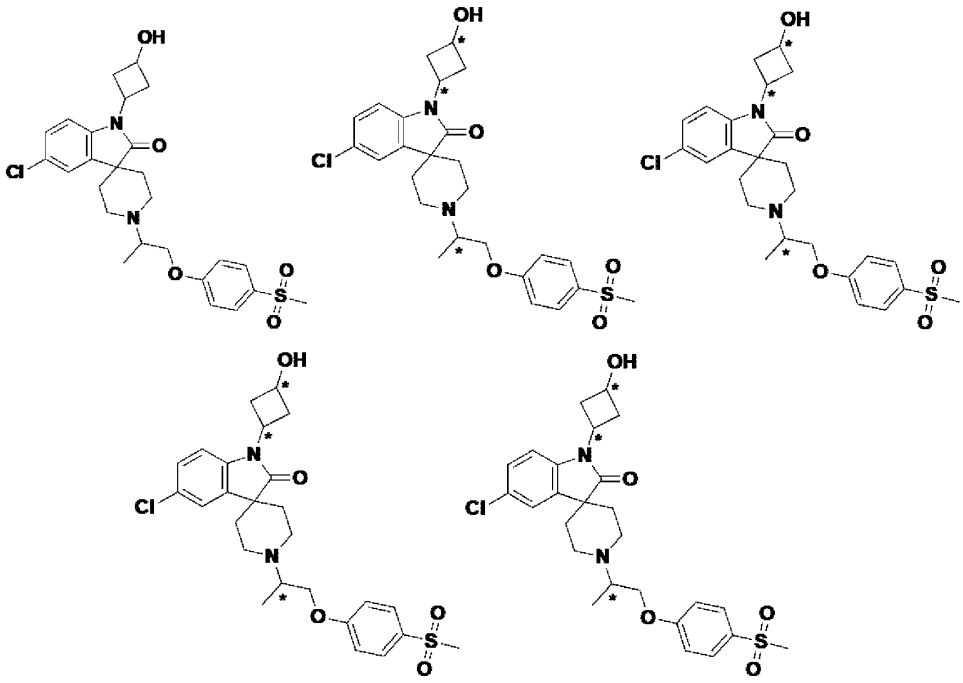
[1098] The following compounds in Table 31 were prepared according to procedures analogous to those described for **Compounds 199–201** using the appropriate starting materials.

[1099] Table 31.

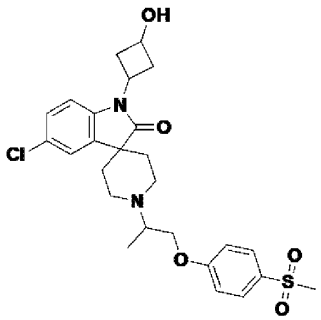
#	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Inter-mediates Used	Chiral Column, If Applicable	Elution Order
202		1'-{1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 445.2 Found 445.2	**A-2** and **B-9**	n/a	n/a
203		(*S*) or (*R*)-1'-{1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 445.2 Found 445.2	**A-2** and **B-9**	Daicel Chiralpak AD-3	First
204		(*R*) *or* (*S*)-1'-{1-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 445.2 Found 445.2	**A-2** and **B-9**	Daicel Chiralpak AD-3	Second

Example 28

5-chloro-1'-[1-(4-methanesulfonylphenoxy)propan-2-yl]-1-[3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 205), 5-chloro-1'-[(2*S*) or (2*R*) -1-(4-methanesulfonylphenoxy)propan-2-yl]-1-[(*cis*) or (*trans*)-3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 206), 5-chloro-1'-[(2*S*) or (2*R*) -1-(4-methanesulfonylphenoxy)propan-2-yl]-1-[(*trans*) or (*cis*)-3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 207), 5-chloro-1'-[(2*R*) or (2*S*) -1-(4-methanesulfonylphenoxy)propan-2-yl]-1-[(*cis*) or (*trans*)-3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 208), and 5-chloro-1'-[(2*R*) or (2*S*) -1-(4-methanesulfonylphenoxy)propan-2-yl]-1-[(*trans*) or (*cis*)-3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 209)

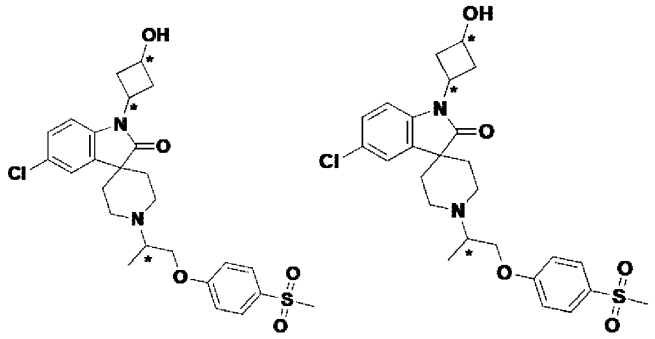


Step 1: 5-chloro-1'-[1-(4-methanesulfonylphenoxy)propan-2-yl]-1-[3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 205)



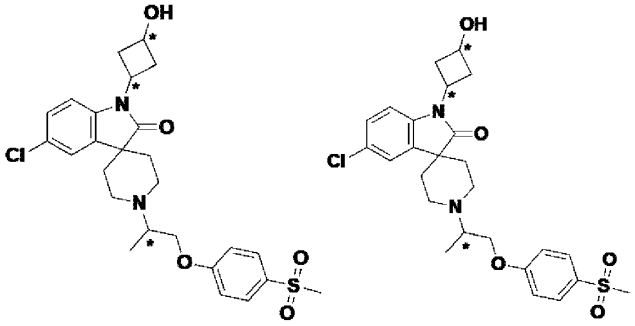
[1100] A mixture of 5-chloro-1-(3-hydroxycyclobutyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-16**, 250 mg, 0.815 mmol), 1-(4-methanesulfonylphenoxy)propan-2-one (**Intermediate A-1**, 465 mg, 2.04 mmol), tetraisopropoxytitanium (231 mg, 0.815 mmol) and AcOH (3.0 mg, 40.7 μmol) in DCE (5 mL) was stirred at room temperature for 1 h. $NaBH(OAc)_3$ (259 mg, 1.22 mmol) was added into the mixture, which was then stirred at 50 °C for 16 h. The reaction mixture was cooled to 0 °C and then quenched with H_2O (20 mL). The mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by reverse phase preparative HPLC (Waters Xbridge BEH C_{18} column, 25–55% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-[1-(4-methanesulfonylphenoxy)propan-2-yl]-1-[3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one as a mixture of diastereomers (**Compound 205**). ^{1}HNMR (400 MHz, DMSO-d_6, 30/31 H): δ 7.85 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 2.0 Hz, 1H), 7.35–7.21 (m, 4H), 5.31 (d, J = 6.8 Hz, 1H), 4.26–4.06 (m, 3H), 3.95–3.90 (m, 1H), 3.16–3.12 (m, 4H), 3.06–2.99 (m, 2H), 2.87–2.71 (m, 2H), 2.64–2.58 (m, 3H), 1.77–1.66 (m, 4H), 1.16 (d, J = 6.8 Hz, 3H). MS = 519.1 $[M+H]^+$.

Step 2: 5-chloro-1'-[(2*S*) or (2*R*) -1-(4-methanesulfonylphenoxy)propan-2-yl]-1-[(cis) or (*trans*)-3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 206) and 5-chloro-1'-[(2*R*) or (2*S*) -1-(4-methanesulfonylphenoxy)propan-2-yl]-1-[(*cis*) or (*trans*)-3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 208)



[1101] 5-chloro-1'-[1-(4-methanesulfonylphenoxy)propan-2-yl]-1-[3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 205**) was separated by preparative chiral SFC (Daicel Chiralcel IG-3, 60% EtOH with 0.1% NH_4OH in CO_2). The first eluting peak contained a mixture of isomers that underwent further chiral separation as described in step 3. The second eluting peak, 5-chloro-1'-[(*2S*) or (*2R*) -1-(4-methanesulfonylphenoxy)propan-2-yl]-1-[(*cis*) or (*trans*)-3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one **(Compound 206):** ^{1}HNMR (400 MHz, DMSO-d_6): δ 7.85 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 2.0 Hz, 1H), 7.30 (dd, J = 8.4, 2.4 Hz, 1H), 7.22 (d, J = 8.8 Hz, 2H), 7.12 (d, J = 8.8 Hz, 1H), 4.93–4.85 (m, 1H), 4.44–4.41 (m, 1H), 4.27–4.22 (m, 1H), 4.10–4.06 (m, 1H), 3.16–3.12 (m, 4H), 3.06–3.00 (m, 2H), 2.92–2.88 (m, 2H), 2.84–2.70 (m, 3H), 2.22–2.15 (m, 2H), 1.77–1.65 (m, 4H), 1.16 (d, J = 6.8 Hz, 3H). MS = 519.1 $[M+H]^+$. The third eluting peak, 5-chloro-1'-[(2*R*) or (2*S*) -1-(4-methanesulfonylphenoxy)propan-2-yl]-1-[(*cis*) or (*trans*)-3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 208**): ^{1}HNMR (400 MHz, DMSO-d_6, 30/31 H): δ 7.85 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 2.0 Hz, 1H), 7.34–7.21 (m, 4H), 5.30 (d, J = 6.4 Hz, 1H), 4.26–4.06 (m, 3H), 3.97–3.89 (m, 1H), 3.16–3.12 (m, 4H), 3.06–3.00 (m, 2H), 2.84–2.72 (m, 2H), 2.65–2.55 (m, 3H), 1.77–1.66 (m, 4H), 1.17–1.15 (m, 3H). MS = 519.1 $[M+H]^+$.

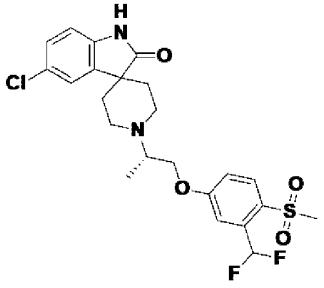
Step 3: 5-chloro-1'-[(2*R*) or (2*S*) -1-(4-methanesulfonylphenoxy)propan-2-yl]-1-[(*trans*) or (*cis*)-3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 209) and 5-chloro-1'-[(2*S*) or (2*R*) -1-(4-methanesulfonylphenoxy)propan-2-yl]-1-[(*trans*) or (*cis*)-3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 207),



[1102] The second eluting peak from Step 2 was further separated by preparative chiral SFC (Daicel Chiralcel OJ-3, 30% MeOH with 0.1% NH_4OH in CO_2). The first eluting isomer, 5-chloro-1'-[(2*R*) or (2*S*) -1-(4-methanesulfonylphenoxy)propan-2-yl]-1-[(*trans*) or (*cis*)-3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 209**): ^{1}HNMR (400 MHz, DMSO-d_6, 30/31 H): δ 7.85 (d, J = 9.2 Hz, 2H), 7.49 (s, 1H), 7.34–7.21 (m, 4H), 5.30 (d, J = 6.8 Hz, 1H), 4.26–4.06 (m, 3H), 3.98–3.89 (m, 1H), 3.16–3.11 (m, 4H), 3.04–3.02 (m, 2H), 2.84–2.72 (m, 2H), 2.67–2.60 (m, 3H), 1.84–1.64 (m, 4H), 1.17–1.15 (m, 3H). MS = 519.1 $[M+H]^+$. The second eluting isomer, 5-chloro-1'-[(2*S*) or (2*R*) -1-(4-methanesulfonylphenoxy)propan-2-yl]-1-[(*trans*) or (*cis*)-3-hydroxycyclobutyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 207**), ^{1}HNMR (400 MHz, DMSO-d_6): δ 7.85 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 2.0 Hz, 1H), 7.30 (dd, J = 8.4, 2.0 Hz, 1H), 7.22 (d, J = 8.8 Hz, 2H), 7.12 (d, J = 8.4 Hz, 1H), 5.16 (d, J = 4.4 Hz, 1H), 4.93–4.85 (m, 1H), 4.44–4.42 (m, 1H), 4.26–4.22 (m, 1H), 4.10–4.06 (m, 1H), 3.16–3.12 (m, 4H), 3.06–3.00 (m, 2H), 2.92–2.72 (m, 4H), 2.22–2.16 (m, 2H), 1.77–1.66 (m, 4H), 1.16 (d, J = 6.8 Hz, 3H). MS = 519.1 $[M+H]^+$.

Example 29A

5-chloro-1'-[(2*S*)-1-[3-(difluoromethyl)-4-methanesulfonylphenoxy]propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 210)

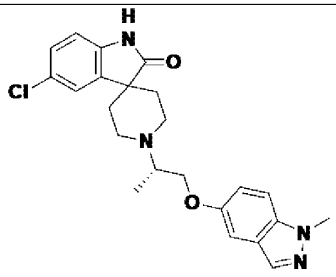
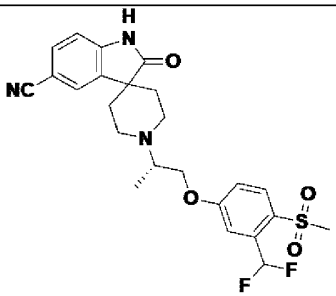
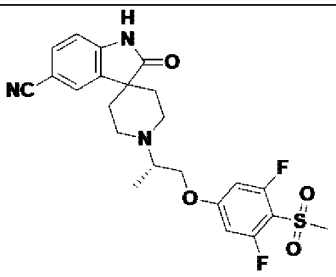


[1103] To a solution containing a mixture of 5-chloro-1'-[(2*S*)-1-hydroxypropan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one and 5-chloro-1'-[(2*R*)-2-hydroxypropyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediates B-17** and **B-18**, 136 mg, 0.461 mmol), 3-(difluoromethyl)-4-methanesulfonylphenol (**Intermediate A-12**, 154 mg, 0.692 mmol) in THF (4 mL) was added PPh_3 (242 mg, 0.923 mmol). The mixture was cooled to 0 °C and DIAD (179 µL, 0.923 mmol) was added dropwise. The mixture was warmed to room temperature and stirred for 15 h. The reaction mixture was quenched with H_2O (8 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 4 g cartridge, 0–90% EtOAc:petroleum ether). The crude product was further purified by reverse phase preparative HPLC (Waters Xbridge BEH C_{18} column, 25–55% MeCN: 10 mM NH_4HCO_3 in H_2O) to give the desired product 5-chloro-1'-[(2*S*)-1-[3-(difluoromethyl)-4-methanesulfonylphenoxy]propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 210**) as the first eluting isomer. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 1H), 8.00 (d, J = 8.8 Hz, 1H), 7.59 (t, J = 54.4 Hz, 1H), 7.44–7.37 (m, 3H), 7.23 (dd, J = 8.0, 2.0 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 4.31 (dd, J = 10.0, 6.4 Hz, 1H), 4.16 (dd, J = 10.0, 5.6 Hz, 1H), 3.26 (s, 3H), 3.18–3.13 (m, 1H), 3.03–3.01 (m, 2H), 2.85–2.73 (m, 2H), 1.80–1.75 (m, 2H), 1.67–1.63 (m, 2H), 1.16 (d, J = 6.8 Hz, 3H). MS = 499.1 $[M+H]^+$.

[1104] The following compounds in Table 32 were prepared according to procedures analogous to those described for **Compound 210** using the appropriate starting materials.

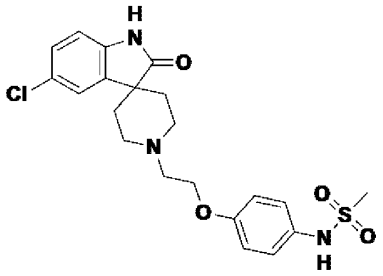
Table 32.

#	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Intermediates Used	Elution Order

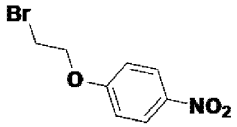
211		5-chloro-1'-[(2*S*)-1-[(1-methyl-1H-indazol-5-yl)oxy]propan-2-yl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 425.2 Found 425.2	**B-17** and **B-18**	First eluting isomer
212		1'-[(2*S*)-1-[3-(difluoromethyl)-4-methanesulfonylphenoxy]propan-2-yl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 490.2 Found 490.2	**A-13, B-19,** and **B-20**	First eluting isomer
213		1'-[(2*S*)-1-(3,5-difluoro-4-methanesulfonylphenoxy)propan-2-yl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 476.1 Found 476.1	**A-11, B-19,** and **B-20**	First eluting isomer

Example 29B

***N*-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]methanesulfonamide (Compound 214)**

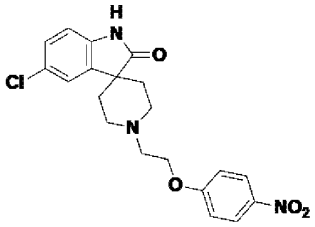


Step 1: 1-(2-bromoethoxy)-4-nitrobenzene



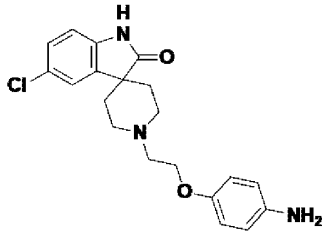
[1105] To a solution of 4-nitrophenol (5.00 g, 35.9 mmol) in 1,2-dibromoethane (30 mL) was added Cs_2CO_3 (35.1 g, 108 mmol). The mixture was stirred at 100°C for 12 h. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–50% EtOAc:petroleum ether) to give 1-(2-bromoethoxy)-4-nitrobenzene. MS = 246.0 / 248.0 $[M+H]^+$.

Step 2: 5-chloro-1'-[2-(4-nitrophenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one



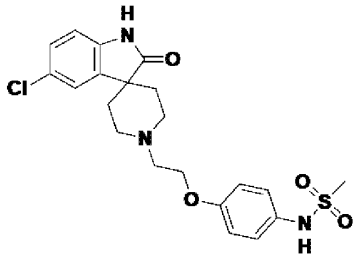
[1106] To a solution of 1-(2-bromoethoxy)-4-nitrobenzene (300 mg, 1.22 mmol) in MeCN (3 mL) was added $NaHCO_3$ (307 mg, 3.66 mmol) and 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 433 mg, 1.58 mmol, HCl salt). The mixture was stirred at 80 °C for 12 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (8 mL) and extracted with EtOAc (3 x 8 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–30% EtOAc:petroleum ether) to give 5-chloro-1'-[2-(4-nitrophenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one. MS = 402.2 $[M+H]^+$.

Step 3: 1'-[2-(4-aminophenoxy)ethyl]-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one



[1107] A mixture of 5-chloro-1'-[2-(4-nitrophenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (200 mg, 498 µmol), Fe (139 mg, 2.49 mmol), and NH_4Cl (79.9 mg, 1.49 mmol) in EtOH (6 mL) and H_2O (2 mL) was stirred at 70 °C for 2 h under a N_2 atmosphere. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo to give 1'-[2-(4-aminophenoxy)ethyl]-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one, which was used in the subsequent step without further purification. MS = 372.2 $[M+H]^+$.

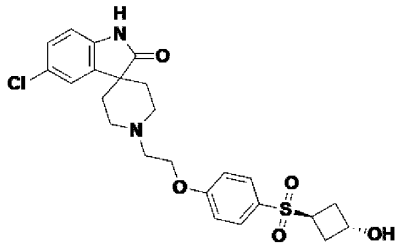
Step 4: *N*-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]methanesulfonamide (Compound 214)



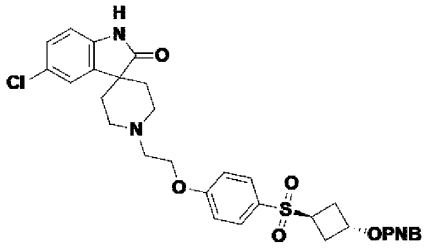
[1108] To a solution of 1'-[2-(4-aminophenoxy)ethyl]-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (110 mg, 296 mmol), and TEA (82.4 µL, 0.52 mmol) in DCM (3 mL) was added methanesulfonic anhydride (103. mg, 0.592 mmol). The mixture was stirred at room temperature for 2 h under N_2 atmosphere. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by reverse phase preparative HPLC (Phenomenex C_{18} column, 20–50% MeCN: 10 mM NH_4HCO_3 in H_2O) to give *N*-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]methanesulfonamide (**Compound 214**). MS = 450.2 $[M+H]^+$.

Example 30

5-chloro-1'-[2-(4-{[(*trans*)-3-hydroxycyclobutyl]sulfonyl}phenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 215)

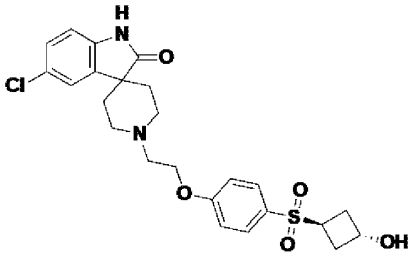


Step 1: (*trans*)-3-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzenesulfonyl]cyclobutyl 4-nitrobenzoate



[1109] To a 0 °C solution of 5-chloro-1'-[2-(4-{[(*cis*)-3-hydroxycyclobutyl]sulfonyl}phenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 17**, 13 mg, 26.5 µmol), 4-nitrobenzoic acid (5.00 mg, 31.8 µmol) and PPh_3 (27 mg, 106 µmol) in THF (2 mL) was added DIAD (20.6 µL, 0.106 mmol). The mixture was stirred at 40 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by preparative TLC (SiO_2, DCM:MeOH = 10:1) to give (*trans*)-3-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzenesulfonyl]cyclobutyl 4-nitrobenzoate. MS = 640.3 $[M+H]^+$.

Step 2: 5-chloro-1'-[2-(4-{[(*trans*)-3-hydroxycyclobutyl]sulfonyl}phenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 215)



[1110] To a 0 °C solution of (*trans*)-3-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzenesulfonyl]cyclobutyl 4-nitrobenzoate (10.0 mg, 15.6 µmol) in THF (2 mL) was added a solution of $LiOH{\cdot}H_2O$ (1.97 mg, 46.9 µmol) in H_2O (0.5 mL). The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by reverse phase preparative HPLC (Waters Xbridge BEH C_{18} column, 20–50% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-[2-(4-{[(*trans*)-3-hydroxycyclobutyl]sulfonyl}phenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one **(Compound 215)**. ^1H NMR (400 MHz, DMSO-d_6): δ 10.50 (s, 1H), 7.80 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 2.0 Hz, 1H), 7.25–7.22 (m, 1H), 7.20 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.4 Hz, 1H), 5.36–5.33 (m, 1H), 4.27–4.21 (m, 3H), 3.89–3.81 (m, 1H), 2.95–2.87 (m, 4H), 2.72–2.67 (m, 4H), 2.18–2.11 (m, 2H), 1.81–1.68 (m, 4H). MS = 491.1 $[M+H]^+$.

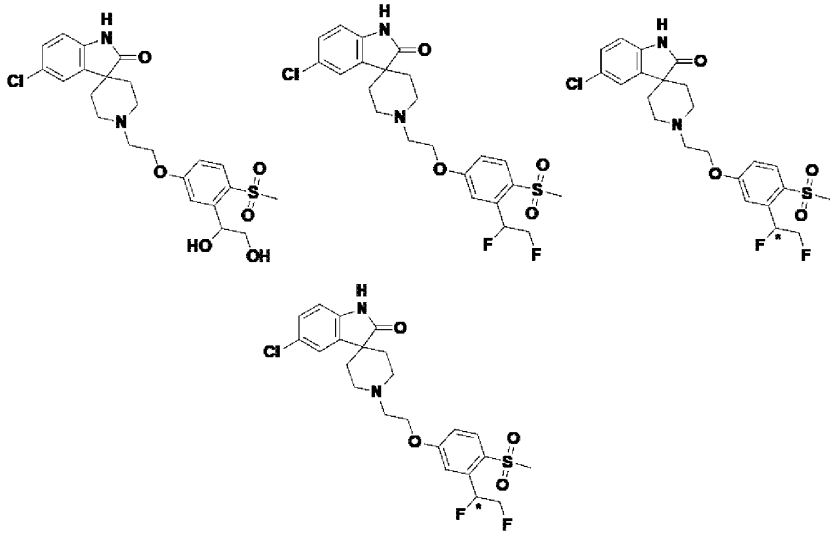
Example 31

5-chloro-1'-{2-[3-(1,2-dihydroxyethyl)-4-methanesulfonylphenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 216)

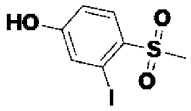
5-chloro-1'-{2-[3-(1,2-difluoroethyl)-4-methanesulfonylphenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 217)

5-chloro-1'-(2-{3-[(1*S* or 1*R*)-1,2-difluoroethyl]-4-methanesulfonylphenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 218) and

5-chloro-1'-(2-{3-[(1*R* or 1*S*)-1,2-difluoroethyl]-4-methanesulfonylphenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 219)

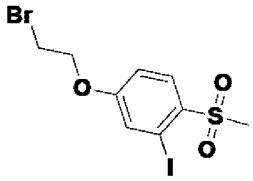


Step 1: 3-iodo-4-methanesulfonylphenol



[1111] To a –20°C solution of 2-iodo-1-methanesulfonyl-4-methoxybenzene (2.00 g, 6.41 mmol) in DCM (30 mL) under N_2 atmosphere was added BBr_3 (1.85 mL, 19.2 mmol) dropwise. The mixture was stirred at room temperature for 6 h. The reaction mixture was cooled to 0 °C, quenched with H_2O (30 mL), and extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give 3-iodo-4-methanesulfonylphenol, which was used in the subsequent step without further purification. MS = 299.0 $[M+H]^+$.

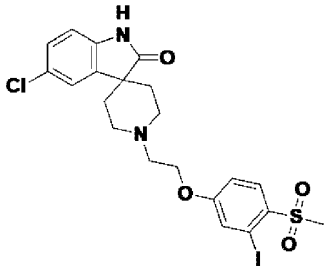
Step 2: 4-(2-bromoethoxy)-2-iodo-1-methanesulfonylbenzene



[1112] To a solution of 3-iodo-4-methanesulfonylphenol (1.90 g, 6.37 mmol) in DMF (5 mL) were added 1,2-dibromoethane (7.21 mL, 95.6 mmol) and K_2CO_3 (2.20 g, 15.9 mmol). The mixture was stirred at 80 °C for 5 h. After cooling to room temperature, the reaction mixture was quenched

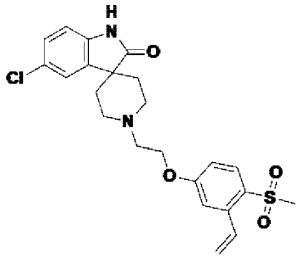
with H_2O (15 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 0–35% EtOAc:petroleum ether) to give 4-(2-bromoethoxy)-2-iodo-1-methanesulfonylbenzene. MS = 404.9 / 406.9 $[M+H]^+$.

Step 3: 5-chloro-1'-[2-(3-iodo-4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one



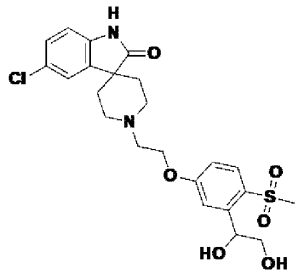
[1113] To a solution of 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 1.38 g, 5.04 mmol, HCl salt) in MeCN (20 mL) was added $NaHCO_3$ (705 mg, 8.39 mmol) and 4-(2-bromoethoxy)-2-iodo-1-methanesulfonylbenzene (1.70 g, 4.20 mmol). The mixture was stirred at 80 °C for 12 h. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 0–100% EtOAc:petroleum ether) to give 5-chloro-1'-[2-(3-iodo-4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one. MS = 561.1 $[M+H]^+$.

Step 4: 5-chloro-1'-[2-(3-ethenyl-4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one



[1114] A solution of potassium vinyltrifluoroborate (1.15 g, 8.56 mmol), 5-chloro-1'-[2-(3-iodo-4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (1.60 g, 2.85 mmol), K_2CO_3 (1.18 g, 8.56 mmol), and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (233 mg, 0.286 mmol) in 1,4-dioxane (15 mL) and H_2O (2 mL) was degassed and purged with N_2 (3x). The mixture was stirred at 100 °C for 12 h under N_2 atmosphere. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–100% EtOAc:petroleum ether) to give 5-chloro-1'-[2-(3-ethenyl-4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one. MS = 461.2 $[M+H]^+$.

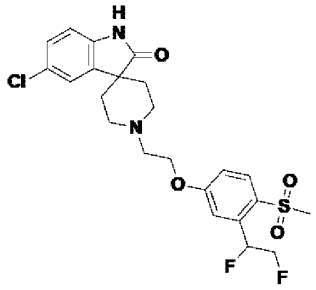
Step 5: 5-chloro-1'-{2-[3-(1,2-dihydroxyethyl)-4-methanesulfonylphenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 216)



[1115] To a 0 °C solution of 5-chloro-1'-[2-(3-ethenyl-4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (1.10 g, 2.39 mmol) in THF (8 mL) and H_2O (2 mL) was added NMO (756 µL, 7.16 mmol) and $K_2OsO_4 \cdot 2H_2O$ (87.9 mg, 0.238 mmol) dropwise. The mixture was stirred at room temperature for 12 h. The reaction mixture was cooled to 0 °C, quenched with H_2O (15 mL), and then extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 0–100% EtOAc:petroleum ether). The crude product was further purified by reverse phase preparative HPLC (Waters Xbridge BEH C_{18} column, 15–45% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-{2-[3-(1,2-dihydroxyethyl)-4-methanesulfonylphenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 216**). ^1H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.51 (s, 1H), 7.27–7.22 (m, 2H), 7.09 (d, J = 8.8 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 5.50 (d, J = 4.8 Hz, 1H), 5.41–5.38 (m, 1H), 4.85 (t, J = 5.6 Hz, 1H), 4.25–4.21 (m, 2H), 3.55–3.53 (m,

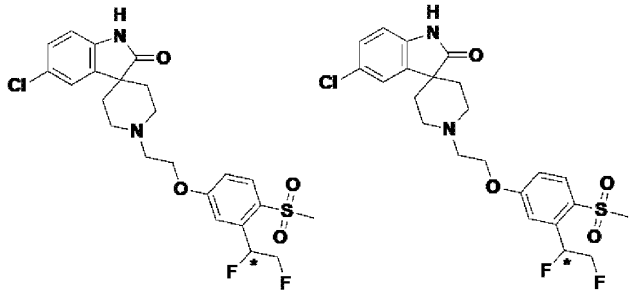
1H), 3.49–3.46 (m, 1H), 3.20 (s, 3H), 2.95–2.87 (m, 4H), 2.72–2.70 (m, 2H), 1.81–1.73 (m, 4H). MS = 495.1 $[M+H]^+$.

Step 6: 5-chloro-1'-{2-[3-(1,2-difluoroethyl)-4-methanesulfonylphenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 217)



[1116] To a –30 °C solution of 5-chloro-1'-{2-[3-(1,2-dihydroxyethyl)-4-methanesulfonylphenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 216**, 300 mg, 0.606 mmol) in THF (5 mL) was added DAST (400 µL, 3.03 mmol). The mixture was allowed to warm to room temperature and stirred for 10 h. The reaction mixture was cooled to 0 °C and quenched with H_2O (10 mL) at 0°C, and then extracted with DCM (2 x 15 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters Xbridge BEH C_{18} column, 15–65% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-{2-[3-(1,2-difluoroethyl)-4-methanesulfonylphenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 217**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 1H), 7.93 (d, J = 8.8 Hz, 1H), 7.50 (s, 1H), 7.29–7.22 (m, 3H), 6.84 (d, J = 8.4 Hz, 1H), 6.62–6.45 (m, 1H), 4.87–4.75 (m, 2H), 4.32–4.27 (m, 2H), 3.29 (s, 3H), 2.93–2.87 (m, 4H), 2.70–2.67 (m, 2H), 1.78–1.72 (m, 4H). MS = 499.1 $[M+H]^+$.

Step 7: 5-chloro-1'-(2-{3-[(1*R* or 1*S*)-1,2-difluoroethyl]-4-methanesulfonylphenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 218) and 5-chloro-1'-(2-{3-[(1*S* or 1*R*)-1,2-difluoroethyl]-4-methanesulfonylphenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 219)

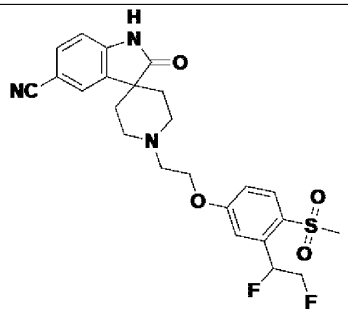
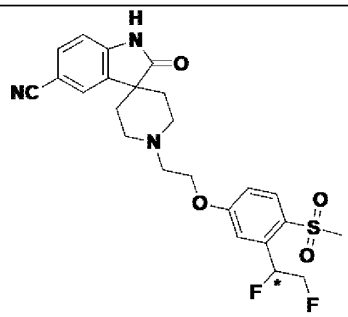
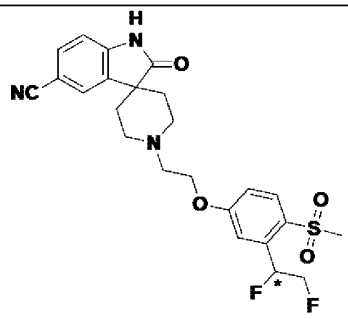


[1117] 5-chloro-1'-{2-[3-(1,2-difluoroethyl)-4-methanesulfonylphenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 217**, 110 mg, 0.216 mmol) was separated by preparative chiral SFC (Daicel Chiralcel OJ-3, 25% EtOH with 0.1% NH_4OH in CO_2). 42% ethanol with 0.1% NH_4OH in CO_2). The second eluting enantiomer of the title compound, Compound **218**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 1H), 7.93 (d, J = 8.8 Hz, 1H), 7.50 (s, 1H), 7.29–7.23 (m, 3H), 6.84 (d, J = 8.0 Hz, 1H), 6.62–6.45 (m, 1H), 4.87–4.75 (m, 2H), 4.32–4.27 (m, 2H), 3.29 (s, 3H), 2.93–2.87 (m, 4H), 2.70–2.67 (m, 2H), 1.78–1.68 (m, 4H). MS = 499.1 $[M+H]^+$. The first eluting enantiomer of the title compound, Compound **219**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 1H), 7.93 (d, J = 8.8 Hz, 1H), 7.50 (s, 1H), 7.29–7.22 (m, 3H), 6.84 (d, J = 8.4 Hz, 1H), 6.62–6.50 (m, 1H), 4.87–4.75 (m, 2H), 4.31–4.27 (m, 2H), 3.29 (s, 3H), 2.93–2.87 (m, 4H), 2.70–2.67 (m, 2H), 1.78–1.72 (m, 4H). MS = 499.1 $[M+H]^+$.

[1118] The following compounds in Table 33 were prepared according to procedures analogous to those described for **Compounds 217–219** using the appropriate starting materials.

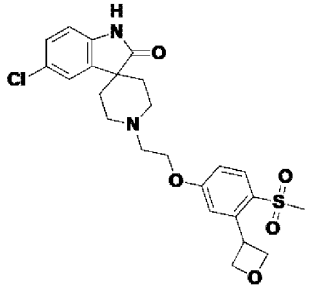
Table 33.

#	Structure	Name	Exact Mass $[M+H]^+$	Inter-mediates Used	Elution Order	Chiral Column
220		1'-{2-[3-(1,2-difluoroethyl)-4-methanesulfonylphenoxy]ethyl}-2-oxo-1,2-	Calc'd 490.2 Found 490.0	**B-9**	n/a	n/a

		dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile				
221		1'-(2-{3-[(1*S* or 1*R*)-1,2-difluoroethyl]-4-methanesulfonylphenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 490.2 Found	**B-9**	Second	Daicel chiralcel OD-3
222		1'-(2-{3-[(1*R* or 1*S*)-1,2-difluoroethyl]-4-methanesulfonylphenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 490.2 Found	**B-9**	First	Daicel Chiralcel OD-3

Example 32

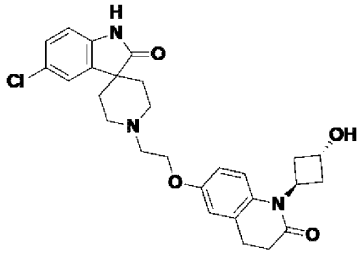
5-chloro-1'-{2-[4-methanesulfonyl-3-(oxetan-3-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 223)



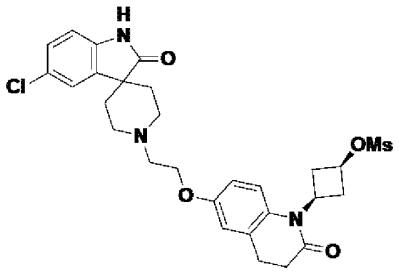
[1119] To a solution of 5-chloro-1'-[2-(3-iodo-4-methanesulfonylphenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Example 31:** Step 3, 100 mg, 0.178 mmol) and 3-iodooxetane (328 mg, 1.78 mmol) in DME (3 mL) under N_2 atmosphere was added nickel(II) chloride ethylene glycol dimethyl ether complex (0.20 mg, 0.91 μmol), 4,4'-di-*tert*-butyl-2,2'-dipyridyl (0.24 mg, 0.89 μmol), (Ir[dF(CF_3)ppy]$_2$(dtbpy))PF_6 (2.0 mg, 1.8 μmol), bis(trimethylsilyl)silyl-trimethyl-silane (55.0 μL, 0.178 mmol) and Na_2CO_3 (37.8 mg, 0.357 mmol). The mixture was stirred at room temperature under 35 W blue LED lights for 15 h. Solids were removed by filtration, and the filtrate was concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex C_{18} column, 20–50% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-{2-[4-methanesulfonyl-3-(oxetan-3-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 223**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 1H), 7.88 (d, J = 8.8 Hz, 1H), 7.51–7.47 (m, 2H), 7.24 (dd, J = 8.0, 2.0 Hz, 1H), 7.13 (dd, J = 8.8, 2.4 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 4.93–4.92 (m, 3H), 4.72–4.69 (m, 2H), 4.32 (t, J = 5.6 Hz, 2H), 3.16 (s, 3H), 2.95–2.89 (m, 4H), 2.74–2.70 (m, 2H), 1.82–1.70 (m, 4H). MS = 491.0 $[M+H]^+$.

Example 33

5-chloro-1'-[2-({2-oxo-1-[(*trans*)-3-hydroxycyclobutyl]-1,2,3,4-tetrahydroquinolin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 224)

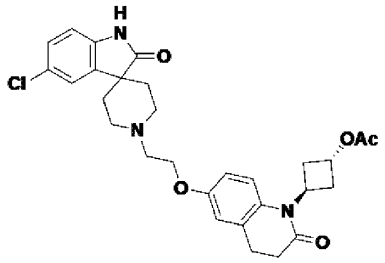


Step 1: (*cis*)-3-[6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-oxo-1,2,3,4-tetrahydroquinolin-1-yl]cyclobutyl methanesulfonate



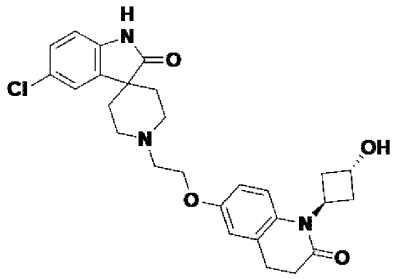
[1120] To a solution of 5-chloro-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxycyclobutyl]-1,2,3,4-tetrahydroquinolin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 114**, 50.0 mg, 0.101 mmol) in DCM (1 mL) was added TEA (28.1 µL, 0.202 mmol). The mixture was cooled to 0 °C and methanesulfonic anhydride (26.3 mg, 0.151 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was cooled to 0 °C, quenched with H_2O (8 mL), and then extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give (*cis*)-3-[6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-oxo-1,2,3,4-tetrahydroquinolin-1-yl]cyclobutyl methanesulfonate, which was used in the subsequent step without further purification. MS = 574.2 $[M+H]^+$.

Step 2: (*trans*)-3-[6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-oxo-1,2,3,4-tetrahydroquinolin-1-yl]cyclobutyl acetate



[1121] To a solution of (*cis*)-3-[6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-oxo-1,2,3,4-tetrahydroquinolin-1-yl]cyclobutyl methanesulfonate (40.0 mg, 69.9 μmol) in DMF (1 mL) was added KOAc (68.4 mg, 0.697 mmol). The mixture was stirred at 100 °C for 12 h. After cooling to 0 °C, the reaction mixture was quenched with H_2O (10 mL), solids were removed by filtration, and the filtrate was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give (*trans*)-3-[6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-oxo-1,2,3,4-tetrahydroquinolin-1-yl]cyclobutyl acetate, which was used in the subsequent step without further purification. MS = 538.3 $[M+H]^+$.

Step 3: 5-chloro-1'-[2-({2-oxo-1-[(*trans*)-3-hydroxycyclobutyl]-1,2,3,4-tetrahydroquinolin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 224)

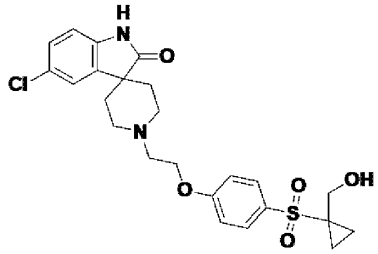


[1122] To a solution of [(*trans*)-3-[6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-oxo-1,2,3,4-tetrahydroquinolin-1-yl]cyclobutyl acetate (40.0 mg, 74.3 μmol) in MeOH (1 mL) was added K_2CO_3 (20.6 mg, 0.149 mmol). The mixture was stirred at room temperature for 6 h. The reaction mixture was filtered to remove solids, and the filtrate was concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters Xbridge BEH C_{18} column, 20–50% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-[2-({2-

oxo-1-[(*trans*)-3-hydroxycyclobutyl]-1,2,3,4-tetrahydroquinolin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 224**). MS = 496.2 $[M+H]^+$.

Example 34

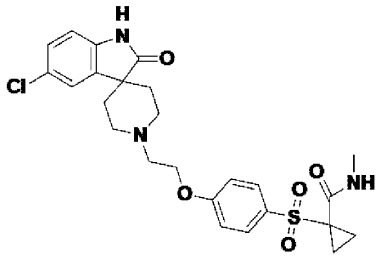
5-chloro-1'-[2-(4-{[1-(hydroxymethyl)cyclopropyl]sulfonyl}phenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 225)



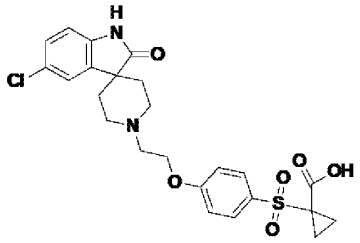
[1123] A solution of methyl 1-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzenesulfonyl]cyclopropane-1-carboxylate (**Compound 91**,180 mg, 0.347 mmol) in THF (3 mL) was degassed and purged with N_2 (3x). The mixture was cooled to 0 °C and 2.0 M $LiBH_4$ in THF (21.4 mL, 42.8 mmol) was added. After stirring at 0 °C for 3 h, the mixture was allowed to warm to room temperature and stirred for another 13 h. The reaction mixture was cooled to 0 °C, quenched with H_2O (5 mL), and then adjusted to pH = 6 with 4.0 M aqueous HCl. The combined organic layers were washed with brine (2 x 6 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters Xbridge BEH C_{18} column, 25–55% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-[2-(4-{[1-(hydroxymethyl)cyclopropyl]sulfonyl}phenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 225**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 2 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.17 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.4 Hz, 1H), 4.85 (t, J = 6.4 Hz, 1H), 4.25 (t, J = 5.6 Hz, 2H), 3.61 (d, J = 6.4 Hz, 2H), 2.93–2.87 (m, 4H), 2.72–2.70 (m, 2H), 1.78–1.72 (m, 4H), 1.30 (t, J = 4.4 Hz, 2H), 1.01 (t, J = 4.8 Hz, 2H). MS = 491.1 $[M+H]^+$.

Example 35

1-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzenesulfonyl]-*N*-methylcyclopropane-1-carboxamide (Compound 226)

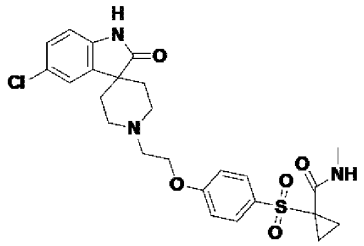


Step 1: 1-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzenesulfonyl]cyclopropane-1-carboxylic acid



[1124] To a solution of methyl 1-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzenesulfonyl]cyclopropane-1-carboxylate (**Compound 91**, 1.30 g, 2.50 mmol) in MeOH (8 mL) and H_2O (8 mL) was added $LiOH \cdot H_2O$ (210 mg, 5.01 mmol). The mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated in vacuo, and the residue was adjusted to pH = 4 with 1.0 M aqueous HCl. The resulting solid was collected via filtration and dried in vacuo to give 1-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzenesulfonyl]cyclopropane-1-carboxylic acid, which was used in the subsequent step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6, 24/25 H): δ 10.55 (s, 1H), 7.90 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 1.6 Hz, 1H), 7.26 (dd, J = 8.4, 3.0 Hz, 1H), 7.10 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.4 Hz, 1H), 4.28 (t, J = 5.2 Hz, 2H), 3.13–3.10 (m, 4H), 2.93–2.90 (m, 2H), 1.86–1.84 (m, 4H), 1.70–1.68 (m, 2H), 1.51–1.49 (m, 2H). MS = 505.0 $[M+H]^+$.

Step 2: 1-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzenesulfonyl]-N-methylcyclopropane-1-carboxamide (Compound 226)

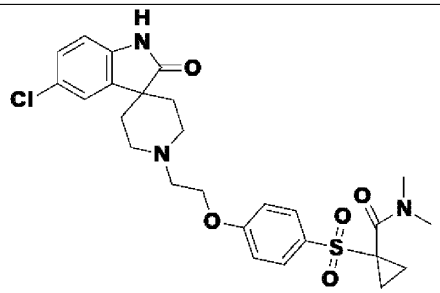
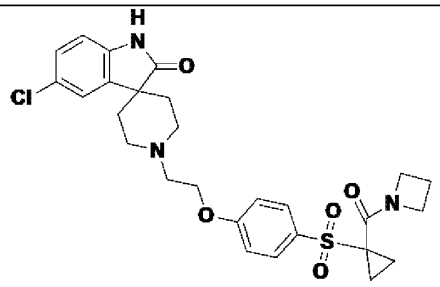


[1125] To a 0 °C solution of 1-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzenesulfonyl]cyclopropane-1-carboxylic acid (120 mg, 0.238 mmol) in DCM (2 mL) was added methylamine hydrochloride (160 mg, 2.38 mmol), TEA (198 µL, 1.43 mmol), and then 60% T3P in EtOAc (252 mg, 0.475 mmol). The mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was quenched with H_2O (8 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex C_{18} column, 20–60% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 1-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzenesulfonyl]-N-methylcyclopropane-1-carboxamide (**Compound 226**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 7.94 (d, J = 4.4 Hz, 1H), 7.82–7.80 (m, 2H), 7.51 (d, J = 2.4 Hz, 1H), 7.24 (dd, J = 8.4, 2.0 Hz, 1H), 7.18–7.16 (m, 2H), 6.85 (d, J = 8.0 Hz, 1H), 4.28 (t, J = 5.6 Hz, 2H), 2.93–2.87 (m, 4H), 2.72–2.69 (m, 2H), 2.59 (d, J = 4.4 Hz, 3H), 1.79–1.74 (m, 4H), 1.59–1.57 (m, 2H), 1.43–1.41 (m, 2H). MS = 518.1 $[M+H]^+$.

[1126] The following compounds in Table 34 were prepared according to procedures similar to step 2 described for **Compound 226** using the appropriate starting materials.

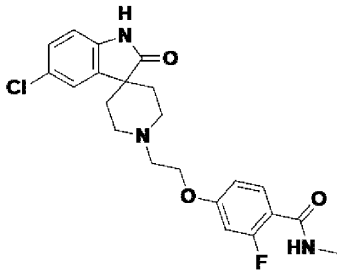
Table 34.

#	Structure	Name	Exact Mass $[M+H]^+$

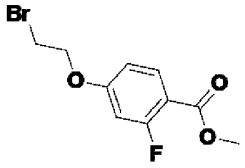
227		1-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)benzenesulfonyl]-N,N-dimethylcyclopropane-1-carboxamide	Calc'd 532.2 Found 532.1
228		1'-[2-(4-{[1-(azetidine-1-carbonyl)cyclopropyl]sulfonyl}phenoxy)ethyl]-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 544.2 Found 544.0

Example 36

4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluoro-N-methylbenzamide (Compound 229)



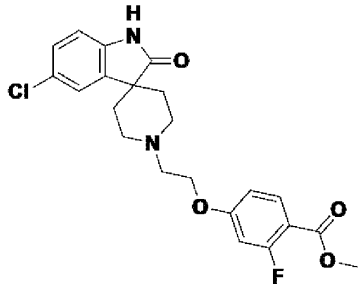
Step 1: methyl 4-(2-bromoethoxy)-2-fluorobenzoate



[1127] To a mixture of methyl 2-fluoro-4-hydroxybenzoate (3.00 g, 17.6 mmol) and 1,2-dibromoethane (6.65 mL, 88.2 mmol) in DMF (20 mL) was added Cs_2CO_3 (11.5 g, 35.3 mmol). The mixture was stirred at 100 °C for 12 h. After cooling to room temperature, the reaction mixture was

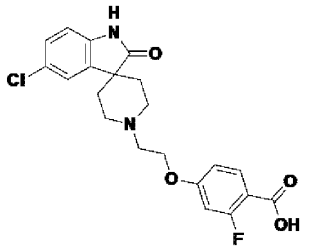
quenched with H_2O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 40 g cartridge, 0–100% EtOAc:petroleum ether) to give methyl 4-(2-bromoethoxy)-2-fluorobenzoate. MS = 277.1 / 279.1 $[M+H]^+$.

Step 2: methyl 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzoate



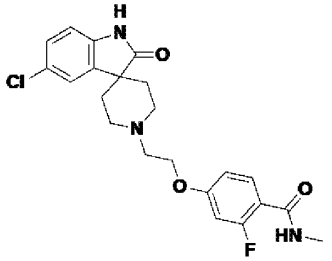
[1128] To a mixture of 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 2.00 g, 7.32 mmol, HCl salt) and methyl 4-(2-bromoethoxy)-2-fluorobenzoate (2.23 g, 8.05 mmol) in MeCN (30 mL) was added $NaHCO_3$ (923 mg, 11.0 mmol). The mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 0–100% EtOAc:petroleum ether) to give methyl 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzoate. MS = 433.2 $[M+H]^+$.

Step 3: 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzoic acid



[1129] To a solution of methyl 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzoate (1.90 g, 4.39 mmol) in THF (15 mL) and H_2O (5 mL) was added $LiOH{\cdot}H_2O$ (315 mg, 13.2 mmol). The mixture was stirred at room temperature for 5 h. The reaction mixture was concentrated in vacuo and adjusted to pH = 4 with 1.0 M aqueous HCl. The resulting solids were collected via filtration and dried in vacuo to give 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzoic acid, which was used in the subsequent step without further purification. MS = 419.1 $[M+H]^+$.

Step 4: 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluoro-N-methylbenzamide (Compound 229)

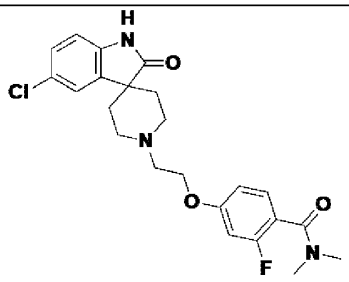
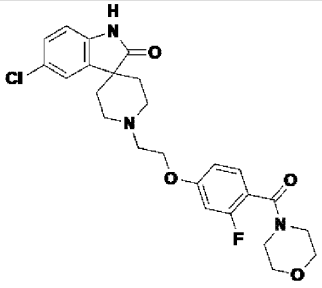
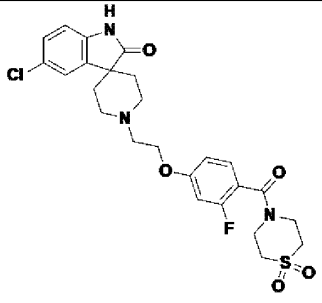


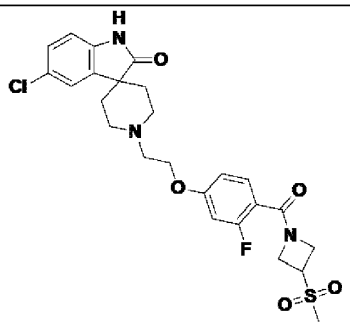
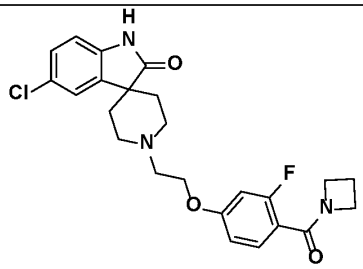
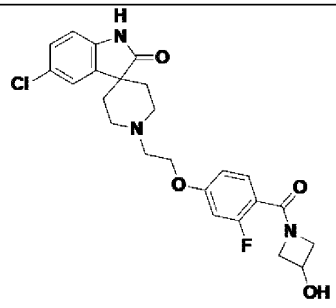
[1130] To a 0 °C solution of 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzoic acid (150 mg, 0.358 mmol) in DCM (2 mL) was added TEA (150 μL, 1.07 mmol), methylamine hydrochloride (96.7 mg, 1.43 mmol), and then 60% T3P in EtOAc (380 mg, 0.716 mmol) dropwise. The mixture was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was cooled to 0 °C, quenched with H_2O (8 mL), and then extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters Xbridge BEH C_{18} column, 15–55% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzoic acid (**Compound 229**). ^1H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 7.99–7.98 (m, 1H), 7.65–7.63 (m, 1H), 7.51 (s, 1H), 7.23 (dd, J = 8.4, 2.0 Hz, 1H), 6.91–6.83 (m, 3H), 4.20 (t, J = 5.6 Hz, 2H), 2.87–2.84 (m, 2H), 2.75 (t, J = 4.4 Hz, 2H), 2.70 (d, J = 4.0 Hz, 3H), 2.69–2.67 (m, 2H), 1.80–1.68 (m, 4H). MS = 432.1 $[M+H]^+$.

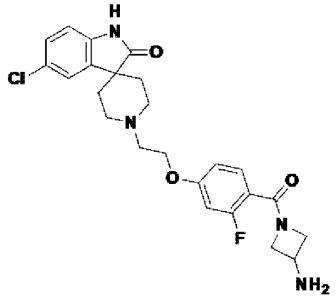
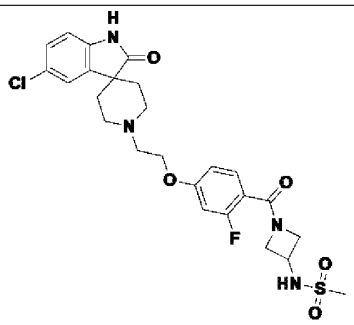
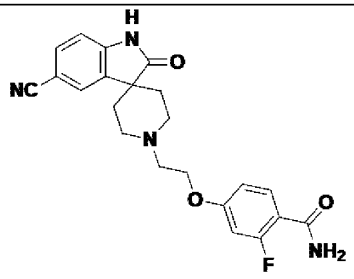
[1131] The following compounds in Table 35 were prepared according to procedures similar to steps 1–4 described for **Compound 229** using the appropriate starting materials. In cases where step

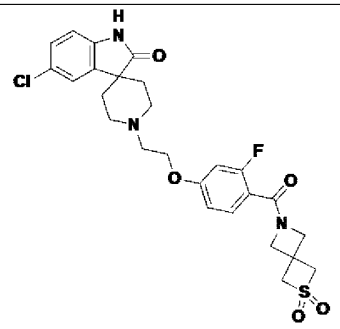
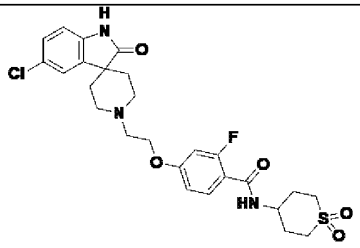
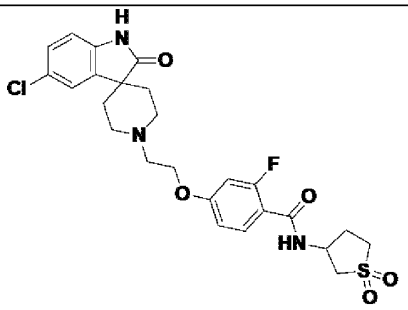
1 was followed by chiral SFC purification to separate isomers, chiral column conditions and elution order are specified.

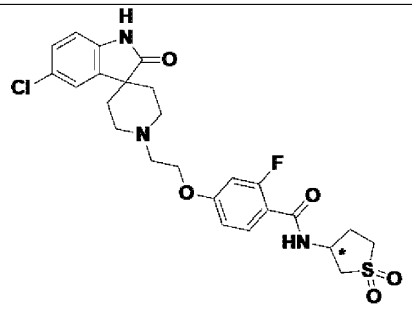
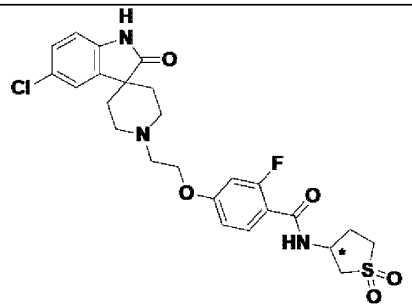
Table 35.

#	Structure	Name	Exact Mass $[M+H]^+$	Elution Order	Chiral Column
230		4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluoro-*N*,*N*-dimethylbenzamide	Calc'd 446.2 Found 446.1	n/a	n/a
231		5-chloro-1'-{2-[3-fluoro-4-(morpholine-4-carbonyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 488.2 Found 488.2	n/a	n/a
232		4-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzoyl]-1λ⁶-	Calc'd 536.1 Found 536.1	n/a	n/a

		thiomorpholine-1,1-dione			
233		5-chloro-1'-{2-[3-fluoro-4-(3-methanesulfonylazetidine-1-carbonyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 536.1 Found 536.1	n/a	n/a
234		1'-{2-[4-(azetidine-1-carbonyl)-3-fluorophenoxy]ethyl}-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 458.2 Found 458.1	n/a	n/a
235		5-chloro-1'-{2-[3-fluoro-4-(3-hydroxyazetidine-1-carbonyl)phenoxy]ethyl}-1,2-dihydrospiro[indol	Calc'd 474.2 Found 474.1	n/a	n/a

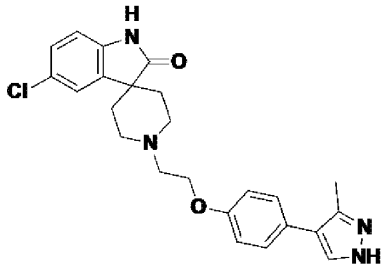
		e-3,4'-piperidin]-2-one			
236		1'-{2-[4-(3-aminoazetidine-1-carbonyl)-3-fluorophenoxy]ethyl}-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 473.2 Found 473.1	n/a	n/a
237		*N*-{1-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzoyl]azetidin-3-yl}methanesulfonamide	Calc'd 551.1 Found 551.2	n/a	n/a
238		4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzamide	Calc'd 409.2 Found 409.2	n/a	n/a

239		6-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzoyl]-2λ⁶-thia-6-azaspiro[3.3]heptane-2,2-dione	Calc'd 548.1 Found 548.2	n/a	n/a
240		4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-(1,1-dioxo-1λ⁶-thian-4-yl)-2-fluorobenzamide	Calc'd 550.2 Found 550.1	n/a	n/a
241		4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-(1,1-dioxo-1λ⁶-thiolan-3-yl)-2-fluorobenzamide	Calc'd 536.1 Found 536.2	n/a	n/a

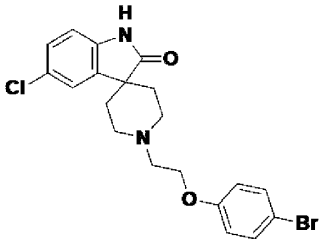
242		4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-[(3*S*) or (3*R*)-1,1-dioxo-1λ⁶-thiolan-3-yl]-2-fluorobenzamide	Calc'd 536.1 Found 536.2	Daicel Chiralpak OD-3	First
243		4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-N-[(3*R*) or (3*S*)-1,1-dioxo-1λ⁶-thiolan-3-yl]-2-fluorobenzamide	Calc'd 536.1 Found 536.2	Daicel Chiralpak OD-3	Second

Example 37

5-chloro-1'-{2-[4-(5-methyl-1H-pyrazol-4-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 244)

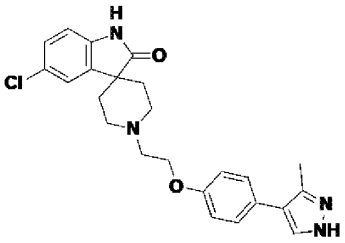


Step 1: 1'-[2-(4-bromophenoxy)ethyl]-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one



[1132] To a solution of 4-bromophenol (300 mg, 1.73 mmol) in acetone (5 mL) was added K_2CO_3 (240 mg, 1.73 mmol), 5-chloro-1'-(2-chloroethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-5**, 778 mg, 2.60 mmol) and NaI (13.0 mg, 86.7 μmol). The mixture was stirred at 50 °C for 16 h. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 4 g cartridge, 0–100% EtOAc:petroleum ether) to give 1'-[2-(4-bromophenoxy)ethyl]-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one. MS = 435.1 / 437.1 $[M+H]^+$.

Step 2: 5-chloro-1'-{2-[4-(5-methyl-1H-pyrazol-4-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 244)

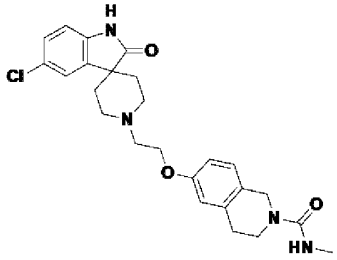


[1133] To a solution of 1'-[2-(4-bromophenoxy)ethyl]-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (200 mg, 0.459 mmol) in *n*-butanol (4 mL) and H_2O (1 mL) was added 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (287 mg, 1.38 mmol), KOAc (135 mg, 1.38 mmol), and bis(4-(di-*tert*-butylphosphanyl)-*N,N*-dimethylaniline) dichloropalladium (6.50 mg, 9.18 μmol). The mixture was degassed and purged with N_2 (3x), and heated via microwave for 2 h at 120 °C. After cooling to room temperature, the mixture was filtered through Celite and the filtrate was concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters Xbridge Prep OBD C_{18} column, 20–50% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-{2-[4-(5-methyl-1H-pyrazol-4-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-

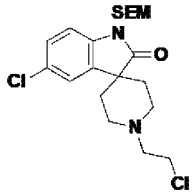
2-one (**Compound 244**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.52 (s, 1H), 10.49 (s, 1H), 7.82–7.59 (m, 1H), 7.52 (s, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 6.4 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.4 Hz, 1H), 4.16–4.13 (m, 2H), 2.87–2.84 (m, 4H), 2.67–2.66 (m, 2H), 2.34–2.29 (m, 3H), 1.79–1.74 (m, 4H). MS = 437.2 $[M+H]^+$.

Example 38

6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-*N*-methyl-1,2,3,4-tetrahydroisoquinoline-2-carboxamide (Compound 245)

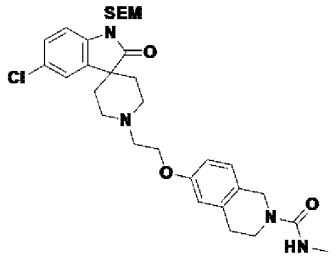


Step 1: 5-chloro-1'-(2-chloroethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one



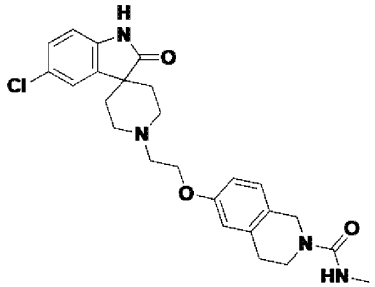
[1134] To a 0 °C solution of 5-chloro-1'-(2-chloroethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-5**, 400 mg, 1.34 mmol) in THF (3 mL) was added NaH (160 mg, 60 wt% in mineral oil, 4.01 mmol). The mixture was stirred at 0 °C for 30 min, and then SEM-Cl (355 μL, 2.01 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred for another 3 h. The reaction mixture was cooled to 0 °C, quenched with saturated aqueous NH_4Cl (10 mL), and then extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–20% EtOAc:petroleum ether) to give 5-chloro-1'-(2-chloroethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one. MS = 429.2 $[M+H]^+$.

Step 2: 6-[2-(5-chloro-2-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl)ethoxy]-*N*-methyl-1,2,3,4-tetrahydroisoquinoline-2-carboxamide



[1135] To a solution of 6-hydroxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline-2-carboxamide (**Intermediate A-81**, 130 mg, 0.630 mmol) in acetone (4 mL) were added K_2CO_3 (87.1 mg, 0.630 mmol), 5-chloro-1'-(2-chloroethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (406 mg, 0.946 mmol), and NaI (4.72 mg, 31.5 μmol). The mixture was stirred at 50 °C for 16 h. Solids were removed by filtration, and the filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 4 g cartridge, 0–100% EtOAc:petroleum ether) to give 6-[2-(5-chloro-2-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl)ethoxy]-*N*-methyl-1,2,3,4-tetrahydroisoquinoline-2-carboxamide. MS = 599.4 $[M+H]^+$.

Step 3: 6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-*N*-methyl-1,2,3,4-tetrahydroisoquinoline-2-carboxamide (Compound 245)

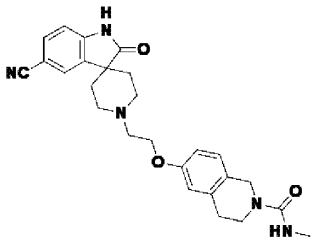


[1136] To a solution of 6-[2-(5-chloro-2-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl)ethoxy]-*N*-methyl-1,2,3,4-tetrahydroisoquinoline-2-carboxamide (230 mg, 0.384 mmol) in DCM (3 mL) was added TFA (1.50 mL, 20.3 mmol). The mixture was stirred at room temperature for 2 h and was then concentrated in vacuo. The residue was dissolved into MeOH (1.5 mL) and 30% NH_4OH solution in H_2O (1.50 mL) was added. Then

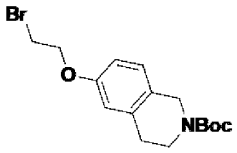
the mixture was stirred at room temperature for 2 h and was then concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex C_{18} column, 15–45% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-*N*-methyl-1,2,3,4-tetrahydroisoquinoline-2-carboxamide (**Compound 245**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 7.51 (s, 1H), 7.23 (d, J = 10.4 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 7.6 Hz, 2H), 6.43 (s, 1H), 4.38 (s, 2H), 4.11–4.10 (m, 2H), 3.49 (t, J = 5.6 Hz, 2H), 2.91–2.85 (m, 2H), 2.84–2.82 (m, 2H), 2.72–2.68 (m, 4H), 2.59 (d, J = 4.4 Hz, 3H), 1.78–1.76 (m, 2H), 1.73–1.71 (m, 2H). MS = 469.2 $[M+H]^+$.

Example 39

6-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-*N*-methyl-1,2,3,4-tetrahydroisoquinoline-2-carboxamide (Compound 246)

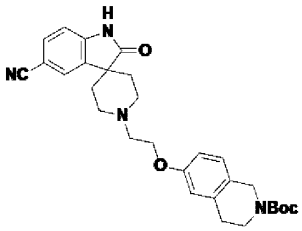


Step 1: *tert*-butyl 6-(2-bromoethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate



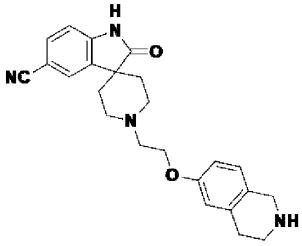
[1137] To a solution of *tert*-butyl 6-hydroxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (500 mg, 2.01 mmol) in 1,2-dibromoethane (15 mL) was added Cs_2CO_3 (1.96 g, 6.02 mmol). The mixture was stirred at 80 °C for 12 h. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Isco 12 g cartridge, 0–40% EtOAc:petroleum ether) to give *tert*-butyl 6-(2-bromoethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate. MS = 302.1 $[M–C_4H_8+H]^+$.

Step 2: *tert*-butyl 6-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate



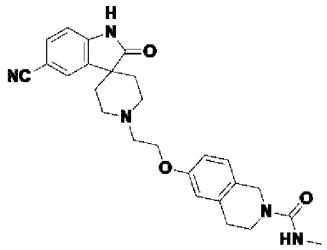
[1138] A mixture of *tert*-butyl 6-(2-bromoethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (100 mg, 0.281 mmol), 2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (**Intermediate B-9**, 74.0 mg, 0.281 mmol, HCl salt) and $NaHCO_3$ (47.0 mg, 0.561 mmol) in MeCN (5 mL) was stirred at 80 °C for 12 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give *tert*-butyl 6-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate, which was taken to the next step without further purification. MS = 448.1 $[M–C_4H_8+H]^+$.

Step 3: 2-oxo-1'-[2-(1,2,3,4-tetrahydroisoquinolin-6-yloxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile



[1139] A solution of *tert*-butyl 6-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (120 mg, 0.239 mmol) in 4.0 M HCl in MeOH (3 mL, 12 mmol) was stirred at room temperature for 2 h. The residue was concentrated in vacuo to give 2-oxo-1'-[2-(1,2,3,4-tetrahydroisoquinolin-6-yloxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile, which was used in the subsequent step without further purification. MS = 403.1 $[M+H]^+$.

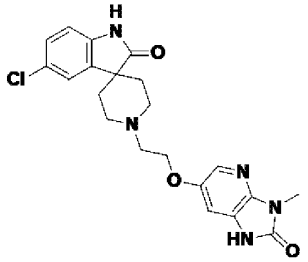
Step 4: 6-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-*N*-methyl-1,2,3,4-tetrahydroisoquinoline-2-carboxamide (Compound 246)



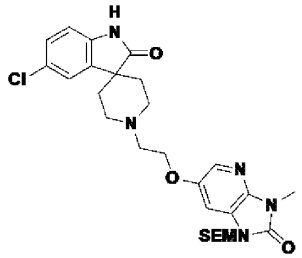
[1140] To a 0 °C solution of 1'-{2-[(2-acetyl-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (140 mg, 0.348 mmol) in DCM (5 mL) was added TEA (96.8 μL, 0.696 mmol) and *N*-methylcarbamoyl chloride (97.6 mg, 1.04 mmol). The mixture was stirred at 0 °C for 2 h, was quenched with H_2O (1 mL), and then extracted with DCM (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex C_{18} column, 15–45% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 6-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-*N*-methyl-1,2,3,4-tetrahydroisoquinoline-2-carboxamide (**Compound 246**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.87 (s, 1H), 7.95 (s, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.03–6.98 (m, 2H), 6.79–6.77 (m, 2H), 6.45–6.44 (m, 1H), 4.38 (s, 2H), 4.10–4.08 (m, 2H), 3.49 (t, J = 6.0 Hz, 2H), 2.74–2.72 (m, 4H), 2.70–2.65 (m, 4H), 2.59 (d, J = 4.4 Hz, 3H), 1.78–1.76 (m, 4H). MS = 460.3 $[M+H]^+$.

Example 40

5-chloro-1'-[2-({3-methyl-2-oxo-1H,2H,3H-imidazo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 247)

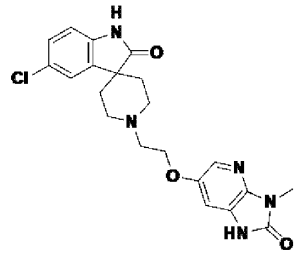


Step 1: 5-chloro-1'-{2-[(3-methyl-2-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H,2H,3H-imidazo[4,5-b]pyridin-6-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one



[1141] To a mixture of 6-(2-bromoethoxy)-3-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H,2H,3H-imidazo[4,5-b]pyridin-2-one (**Intermediate A-74**, 150 mg, 0.373 mmol) and 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 112 mg, 0.410 mmol, HCl salt) in MeCN (3 mL) was added $NaHCO_3$ (47.0 mg, 0.559 mmol). The mixture was stirred at 80 °C for 12 h. After cooling to room temperature, the reaction mixture was poured into H_2O (5 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 4 g cartridge, 0–100% EtOAc:petroleum ether) to give 5-chloro-1'-{2-[(3-methyl-2-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H,2H,3H-imidazo[4,5-b]pyridin-6-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one. MS = 558.3 $[M+H]^+$.

Step 2: 5-chloro-1'-[2-({3-methyl-2-oxo-1H,2H,3H-imidazo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 247)

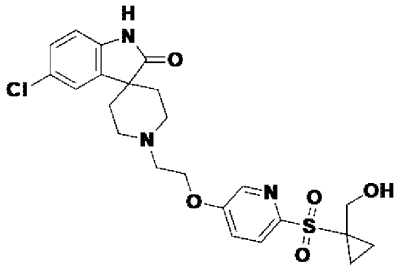


[1142] A solution of 5-chloro-1'-{2-[(3-methyl-2-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H,2H,3H-imidazo[4,5-b]pyridin-6-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (100 mg, 0.179 mmol) in DCM (2 mL) and TFA (0.5 mL) was stirred at room temperature for 1 h. The reaction mixture was concentrated in vacuo, then dissolved in MeOH (3 mL) and 25% NH_4OH solution in H_2O (1 mL) was added. The mixture was stirred at room temperature for 1 h, was diluted with H_2O (5 mL), and then extracted with EtOAc (2 x 10 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. The crude residue was purified by reverse phase

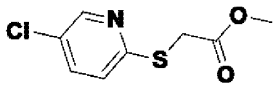
preparative HPLC (Phenomenex C_{18} column, 15–45% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-[2-({3-methyl-2-oxo-1H,2H,3H-imidazo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 247**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.03 (s, 1H), 10.48 (s, 1H), 7.71 (d, J = 2.4 Hz, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.23 (dd, J = 8.0, 2.0 Hz, 1H), 7.04 (d, J = 2.4 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 4.16 (t, J = 5.6 Hz, 2H), 3.26 (s, 3H), 2.95–2.87 (m, 2H), 2.84 (t, J = 5.6 Hz, 2H), 2.72–2.65 (m, 2H), 1.84–1.75 (m, 2H), 1.74–1.66 (m, 2H). MS = 428.1 $[M+H]^+$.

Example 41

5-chloro-1'-{2-[(6-{[1-(hydroxymethyl)cyclopropyl]sulfonyl}pyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 248)

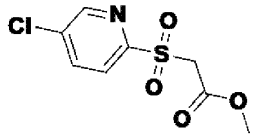


Step 1: methyl 2-[(5-chloropyridin-2-yl)sulfanyl]acetate



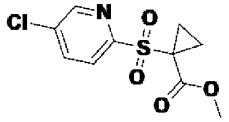
[1143] A mixture of 5-chloropyridine-2-thiol (3.00 g, 20.6 mmol), methyl 2-bromoacetate (2.92 mL, 30.9 mmol), and K_2CO_3 (5.69 g, 41.2 mmol) in DMF (50 mL) was degassed and purged with N_2 (3x). The mixture was stirred at room temperature for 2 h under N_2 atmosphere. The reaction mixture was quenched with H_2O (30 mL) and then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 40 g cartridge, 0–5% EtOAc:petroleum ether) to give methyl 2-[(5-chloropyridin-2-yl)sulfanyl]acetate. MS = 218.0 $[M+H]^+$.

Step 2: methyl 2-[(5-chloropyridin-2-yl)sulfonyl]acetate



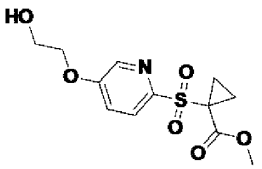
[1144] A mixture of methyl 2-[(5-chloropyridin-2-yl)sulfanyl]acetate (5.70 g, 26.2 mmol), *m*-CPBA (10.6 g, 85% purity, 52.4 mmol) in DCM (2 mL) was degassed and purged with N_2 (3x). The mixture was stirred at 0 °C for 2 h under N_2 atmosphere. The reaction mixture was quenched with saturated Na_2SO_3 (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 40 g cartridge, 0–13% EtOAc:petroleum ether) to give methyl 2-[(5-chloropyridin-2-yl)sulfonyl]acetate. MS = 250.0 $[M+H]^+$.

Step 3: methyl 1-[(5-chloropyridin-2-yl)sulfonyl]cyclopropane-1-carboxylate



[1145] A mixture of methyl 2-[(5-chloropyridin-2-yl)sulfonyl]acetate (5.00 g, 20.0 mmol), 1,2-dibromoethane (1.81 mL, 24.0 mmol), and K_2CO_3 (6.92 g, 50.1 mmol) in DMF (50 mL) was degassed and purged with N_2 (3x). The mixture was stirred at 60 °C for 10 h under N_2 atmosphere. After cooling to room temperature, the mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 40 g cartridge, 0–60% EtOAc:petroleum ether) to give methyl 1-[(5-chloropyridin-2-yl)sulfonyl]cyclopropane-1-carboxylate. MS = 276.0 $[M+H]^+$.

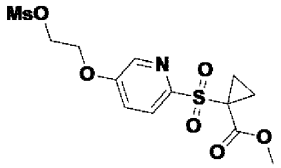
Step 4: methyl 1-{[5-(2-hydroxyethoxy)pyridin-2-yl]sulfonyl}cyclopropane-1-carboxylate



[1146] A mixture of methyl 1-[(5-chloropyridin-2-yl)sulfonyl]cyclopropane-1-carboxylate (5.00 g, 18.1 mmol), ethylene glycol (20.3 mL, 363 mmol), and Cs_2CO_3 (17.7 g, 54.4 mmol) in DMSO (2

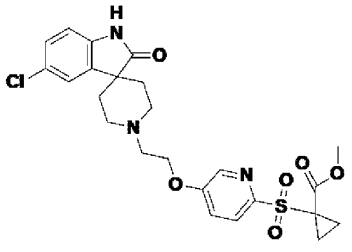
mL) was degassed and purged with N_2 (3x). The mixture was stirred at 100 °C for 12 h under N_2 atmosphere. After cooling to room temperature, MeI (3.39 mL, 54.4 mmol) was added, and the mixture was stirred for 12 h. The mixture was quenched with H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 40 g cartridge, 0–60% EtOAc:petroleum ether) to give methyl 1-{[5-(2-hydroxyethoxy)pyridin-2-yl]sulfonyl}cyclopropane-1-carboxylate. MS = 302.2 $[M+H]^+$.

Step 5: methyl 1-({5-[2-(methanesulfonyloxy)ethoxy]pyridin-2-yl}sulfonyl)cyclopropane-1-carboxylate



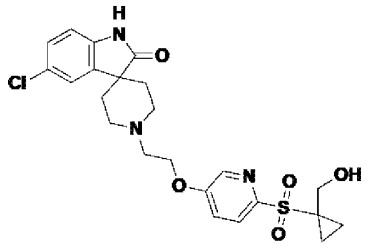
[1147] To a 0 °C mixture of methyl 1-{[5-(2-hydroxyethoxy)pyridin-2-yl]sulfonyl}cyclopropane-1-carboxylate (500 mg, 1.66 mmol) and TEA (0.693 mL, 4.98 mmol) in DCM (2 mL) was added methanesulfonic anhydride (578 mg, 3.32 mmol). The mixture was stirred at 0 °C for 2 h. The mixture was quenched with H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 40 g cartridge, 0–60% EtOAc:petroleum ether) to give methyl 1-({5-[2-(methanesulfonyloxy)ethoxy]pyridin-2-yl}sulfonyl)cyclopropane-1-carboxylate. MS =380.1 $[M+H]^+$.

Step 6: methyl 1-{[5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)pyridin-2-yl]sulfonyl}cyclopropane-1-carboxylate



[1148] A mixture of methyl 1-({5-[2-(methanesulfonyloxy)ethoxy]pyridin-2-yl}sulfonyl)cyclopropane-1-carboxylate (700 mg, 1.84 mmol), 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 605 mg, 2.21 mmol, HCl salt), and $NaHCO_3$ (310 mg, 3.69 mmol) in MeCN (10 mL) was degassed and purged with N_2 (3x). The mixture was stirred at 80 °C for 12 h under N_2 atmosphere. After cooling to room temperature, the mixture was quenched with H_2O (50 mL) and then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–80% EtOAc:petroleum ether) to give methyl 1-{[5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)pyridin-2-yl]sulfonyl}cyclopropane-1-carboxylate. MS = 520.2 $[M+H]^+$.

Step 7: 5-chloro-1'-{2-[(6-{[1-(hydroxymethyl)cyclopropyl]sulfonyl}pyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 248)

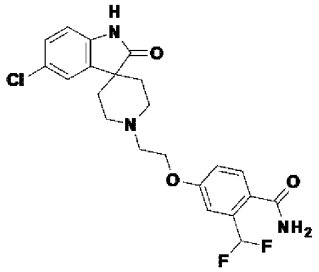


[1149] To a 0 °C solution of methyl 1-{[5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)pyridin-2-yl]sulfonyl}cyclopropane-1-carboxylate (100 mg, 0.192 mmol) in THF (2 mL) was added $LiAlH_4$ (14.6 mg, 385 mmol). The reaction mixture allowed to warm to room temperature and stirred for 2 h under N_2 atmosphere. The mixture was quenched with H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters Xbridge BEH C_{18} column, 25–55% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-{2-[(6-{[1-(hydroxymethyl)cyclopropyl]sulfonyl}pyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 248**). ^1H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 8.48 (d, J = 2.8 Hz, 1H), 7.97 (d, J = 8.8 Hz, 1H), 7.68 (dd, J = 8.8, 2.8 Hz, 1H), 7.50 (s, 1H), 7.24–7.22 (m, 1H), 6.84 (d, J = 8.4 Hz, 1H), 4.82 (t, J = 6 Hz, 1H), 4.33 (t, J = 6 Hz, 2H), 3.70 (d, J = 6 Hz, 2H),

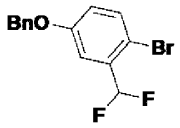
2.98 –2.85 (m, 4H), 2.79–2.68 (m, 2H), 1.83–1.67 (m, 4H), 1.39–1.30 (m, 2H), 1.09–1.02 (m, 2H). MS = 492.2 $[M+H]^+$.

Example 42

4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(difluoromethyl)benzamide (Compound 249)

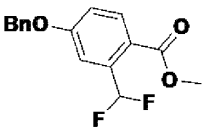


Step 1: 4-(benzyloxy)-1-bromo-2-(difluoromethyl)benzene



[1150] To a 0 °C solution of 5-(benzyloxy)-2-bromobenzaldehyde (3.00 g, 10.3 mmol) in DCM (30 mL) was added DAST (2.72 mL, 20.6 mmol). The mixture was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was cooled to 0 °C, quenched with saturated $NaHCO_3$ aqueous solution (20 mL), diluted with H_2O (10 mL), and then extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 0–20% EtOAc:petroleum ether) to give 4-(benzyloxy)-1-bromo-2-(difluoromethyl)benzene.

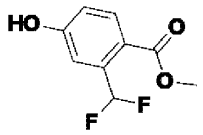
Step 2: methyl 4-(benzyloxy)-2-(difluoromethyl)benzoate



[1151] A mixture of 4-(benzyloxy)-1-bromo-2-(difluoromethyl)benzene (2.20 g, 7.03 mmol), $Pd(OAc)_2$ (315 mg, 1.41 mmol), and 1,1'-bis(diphenylphosphino)ferrocene (1.56 g, 2.81 mmol) in MeOH (15 mL) and toluene (15 mL) was degassed and purged with N_2 (3x). The suspension was

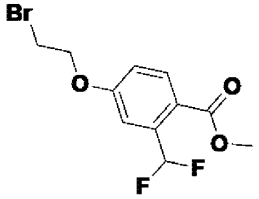
then degassed under vacuum and purged with CO. The mixture was stirred under CO (50 psi) at 80 °C for 12 h. After cooling to room temperature, solids were removed by filtration, and the filtrate was concentrated in vacuo. The residue was taken up in H_2O (40 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (2 x 12 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Isco 20 g cartridge, 0–23% EtOAc:petroleum ether) to give methyl 4-(benzyloxy)-2-(difluoromethyl)benzoate. MS = 293.1 $[M+H]^+$.

Step 3: methyl 2-(difluoromethyl)-4-hydroxybenzoate



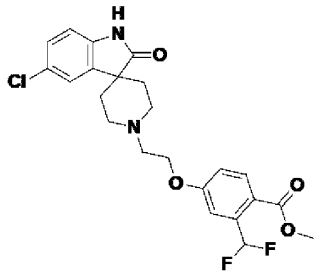
[1152] To a solution of methyl 4-(benzyloxy)-2-(difluoromethyl)benzoate (420 mg, 1.44 mmol) in MeOH (10 mL) under N_2 atmosphere was added Pd/C (100 mg, 10 wt%, 0.0940 mmol) and $Pd(OH)_2/C$ (100 mg, 20 wt%, 0.140 mmol). The mixture was stirred at 50 °C for 12 h under H_2 (50 Psi) atmosphere. After cooling to room temperature, the reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Isco 12 g cartridge, 0–30% EtOAc:petroleum ether) to give methyl 2-(difluoromethyl)-4-hydroxybenzoate. MS = 203.1 $[M+H]^+$.

Step 4: methyl 4-(2-bromoethoxy)-2-(difluoromethyl)benzoate



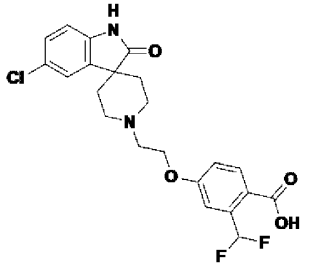
[1153] To a solution of methyl 2-(difluoromethyl)-4-hydroxybenzoate (300 mg, 1.48 mmol) in 1,2- dibromoethane (5 mL) was added Cs_2CO_3 (1.45 g, 4.45 mmol). The mixture was stirred at 100 °C for 12 h. After cooling to room temperature, the mixture was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Isco 4 g cartridge, 0–50% EtOAc:petroleum ether) to give methyl 4-(2-bromoethoxy)-2-(difluoromethyl)benzoate.

Step 5: methyl 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(difluoromethyl)benzoate



[1154] A mixture of methyl 4-(2-bromoethoxy)-2-(difluoromethyl)benzoate (200 mg, 0.647 mmol), 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 177 mg, 0.647 mmol, HCl salt) and $NaHCO_3$ (163 mg, 1.94 mmol) in MeCN (4 mL) was degassed and purged with N_2 (3 times). The mixture was stirred at 80 °C for 12 h under N_2 atmosphere. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Isco 12 g cartridge, 0–50% EtOAc:petroleum ether) to give methyl 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(difluoromethyl)benzoate. MS = 465.1 $[M+H]^+$.

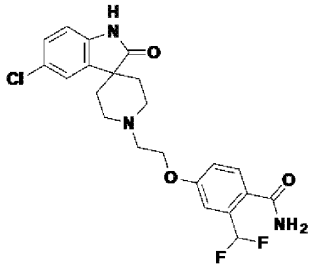
Step 6: 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(difluoromethyl)benzoic acid



[1155] To a solution of methyl 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(difluoromethyl)benzoate (200 g, 430 mmol) in MeOH (4 mL) was added a solution of $LiOH \cdot H_2O$ (144 mg, 3.44 mmol) in H_2O (4 mL). The mixture was stirred at 50 °C for 2 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo to remove MeOH. The residue was adjusted to pH = 2–3 with 1.0 M aqueous HCl solution. The resulting solids were isolated by filtration, and then dried in vacuo. The crude product was triturated with H_2O and then

dried again in vacuo to give 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(difluoromethyl)benzoic acid, which was used in the subsequent step without further purification. MS = 451.1 $[M+H]^+$.

Step 7: 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(difluoromethyl)benzamide (Compound 249)

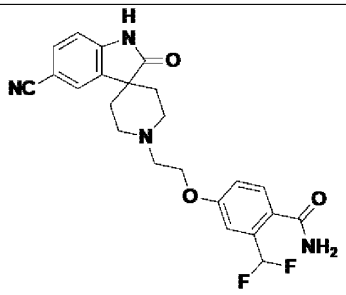


[1156] To a 0 °C solution of 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(difluoromethyl)benzoic acid (200 mg, 0.444 mmol) in DMF (20 mL) was added NH_4Cl (71.2 mg, 1.33 mmol), TEA (216 µL, 1.55 mmol), and then HATU (202 mg, 0.532 mmol). The mixture was allowed to warm to room temperature, stirred for 12 h, and then quenched with H_2O (15 mL). Solids were removed by filtration, and the filtrate was concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters Xbridge Prep OBD C_{18} column, 25–55% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(difluoromethyl)benzamide (**Compound 249**). ^1H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 7.96 (s, 1H), 7.71–7.61 (m, 1H), 7.52–7.32 (m, 3H), 7.25–7.14 (m, 3H), 6.84 (d, J = 8.4 Hz, 1H), 4.24 (t, J = 5.6 Hz, 2H), 2.97–2.83 (m, 4H), 2.74–2.68 (m, 2H), 1.83–1.66 (m, 4H). MS = 450.1 $[M+H]^+$.

[1157] The following compounds in Table 36 were prepared according to procedures similar to steps 1–7 described for **Compound 249** using the appropriate starting materials.

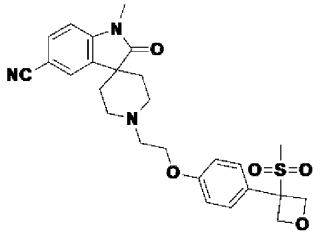
Table 36.

#	Structure	Name	Exact Mass $[M+H]^+$	Intermediate Used

250		4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(difluoromethyl)benzamide	Calc'd 441.2 Found 441.1	**B-9**

Example 43

1'-{2-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (Compound 251)

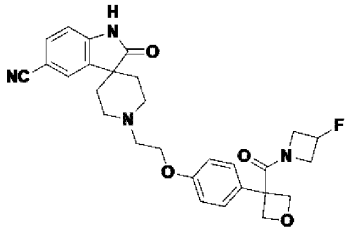


[1158] To a 0 °C solution of 1'-{2-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (**Compound 109**, 78.0 mg, 0.162 mmol) in DMA (1 mL) was added NaH (13.0 mg, 60 wt% in mineral oil, 0.324 mmol) portionwise. The mixture was stirred at 0 °C for 30 min, and then MeI (11.1 μL, 0.178 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was quenched with H_2O (10 mL) and then extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex C_{18} column, 20–50% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 1'-{2-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]ethyl}-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (**Compound 251**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99 (d, J = 1.2 Hz, 1H), 7.80 (dd, J = 8.0, 1.6 Hz, 1H), 7.26 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 8.8 Hz, 2H), 5.21 (d, J = 7.6 Hz, 2H), 5.01 (d, J = 7.6

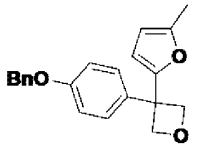
Hz, 2H), 4.18 (t, J = 5.6 Hz, 2H) 3.16 (s, 3H), 2.96–2.88 (m, 4H), 2.86 (s, 3H), 2.79–2.76 (m, 2H), 1.82–1.77 (m, 4H). MS = 496.2 $[M+H]^+$.

Example 44

1'-(2-{4-[3-(3-fluoroazetidine-1-carbonyl)oxetan-3-yl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (Compound 252)

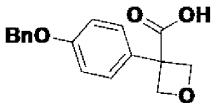


Step 1: 2-{3-[4-(benzyloxy)phenyl]oxetan-3-yl}-5-methylfuran



[1159] To a solution 3-[4-(benzyloxy)phenyl]oxetan-3-ol (**Intermediate A-35**, 20.0 g, 78.0 mmol) in $CHCl_3$ (200 mL) was added tetrabutylammonium hexafluorophosphate (1.66 g, 4.29 mmol), [bis(trifluoromethylsulfonyl)amino]lithium (2.46 g, 8.58 mmol), and 2-methylfuran (35.1 mL, 390 mmol). The mixture was stirred at 50 °C for 4 h. After cooling to 0 °C, the reaction mixture was quenched with H_2O (200 mL) and extracted with DCM (3 x 200 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 220 g cartridge, 0–15% EtOAc:petroleum ether) to give 2-{3-[4-(benzyloxy)phenyl]oxetan-3-yl}-5-methylfuran. MS = 321.2 $[M+H]^+$.

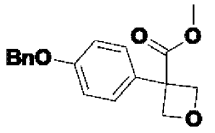
Step 2: 3-[4-(benzyloxy)phenyl]oxetane-3-carboxylic acid



[1160] To a solution of 2-{3-[4-(benzyloxy)phenyl]oxetan-3-yl}-5-methylfuran (11.0 g, 34.3 mmol) in heptane (200 mL), EtOAc (200 mL) and H_2O (400 mL) was added $NaIO_4$ (51.4 g, 240 mmol) and $RuCl_3$ (178 mg, 0.858 mmol). The mixture was stirred at room temperature for 16 h. The reaction mixture was cooled to 0 °C and quenched with saturated Na_2SO_3 (200 mL). The mixture

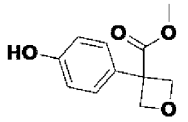
was adjusted to pH = 8 with saturated $NaHCO_3$ and washed with EtOAc (3 x 400 mL). The aqueous layer was adjusted to pH = 2–3 with 2.0 M aqueous HCl solution and extracted with EtOAc (3 x 400 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give 3-[4-(benzyloxy)phenyl]oxetane-3-carboxylic acid, which was used in the subsequent step without further purification. MS = 283.0 $[M–H]^-$.

Step 3: methyl 3-[4-(benzyloxy)phenyl]oxetane-3-carboxylate



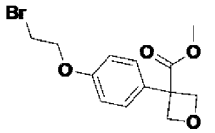
[1161] To a solution of 3-[4-(benzyloxy)phenyl]oxetane-3-carboxylic acid (4.00 g, 14.1 mmol) in DMF (50 mL) was added K_2CO_3 (2.92 g, 21.1 mmol) and MeI (4.38 mL, 70.5 mmol). The mixture was stirred at room temperature for 3 h. The reaction mixture was cooled to 0 °C, quenched with H_2O (100 mL), and the resulting precipitate was collected by filtration and washed with H_2O to give methyl 3-[4-(benzyloxy)phenyl]oxetane-3-carboxylate, which was used in the subsequent step without further purification. MS = 316.2 $[M+NH_4]^+$.

Step 4: methyl 3-(4-hydroxyphenyl)oxetane-3-carboxylate



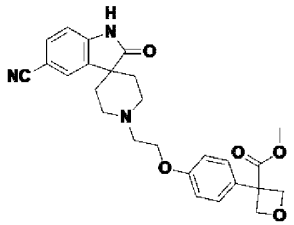
[1162] To a solution of methyl 3-[4-(benzyloxy)phenyl]oxetane-3-carboxylate (4.00 g, 13.4 mmol) in EtOAc (100 mL) under N_2 atmosphere was added Pd/C (5.00 g, 10 wt%, 4.70 mmol). The suspension was degassed under vacuum and purged with H_2 (3x). After stirring under an atmosphere of H_2 (15 psi) at room temperature for 4 h, solids were removed by filtration through Celite and the filtrate was concentrated in vacuo to give methyl 3-(4-hydroxyphenyl)oxetane-3-carboxylate, which was used in the subsequent step without further purification. MS = 231.1 $[M+Na]^+$.

Step 5: methyl 3-[4-(2-bromoethoxy)phenyl]oxetane-3-carboxylate



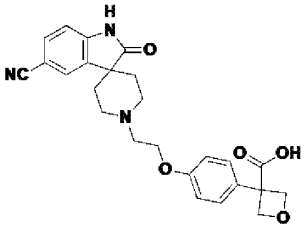
[1163] To a solution of methyl 3-(4-hydroxyphenyl)oxetane-3-carboxylate (2.20 g, 10.6 mmol) in DMF (3 mL) was added 1,2-dibromoethane (17.0 mL, 225 mmol) and Cs_2CO_3 (6.89 g, 21.1 mmol). The mixture was stirred at 100 °C for 6 h. After cooling to 0 °C, the reaction mixture was quenched with H_2O (30 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 45 g cartridge, 0–40% EtOAc:petroleum ether) to give methyl 3-[4-(2-bromoethoxy)phenyl]oxetane-3-carboxylate. MS = 332.1 / 334.1 $[M+NH_4]^+$.

Step 6: methyl 3-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]oxetane-3-carboxylate



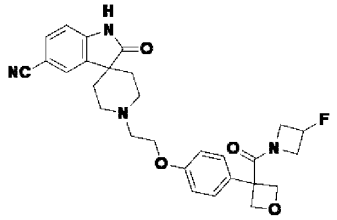
[1164] To a solution of methyl 3-[4-(2-bromoethoxy)phenyl]oxetane-3-carboxylate (2.50 g, 7.93 mmol) in MeCN (30 mL) was added $NaHCO_3$ (2.00 g, 23.8 mmol) and 2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (**Intermediate B-9**, 2.09 g, 7.93 mmol, HCl salt). The mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was filtered and washed with MeCN (40 mL) and EtOAc (20 mL). The filtrate was concentrated in vacuo to give methyl 3-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]oxetane-3-carboxylate, which was used in the subsequent step without further purification. MS = 462.2 $[M+H]^+$.

Step 7: 3-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]oxetane-3-carboxylic acid



[1165] To a solution of methyl 3-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]oxetane-3-carboxylate (3.00 g, 6.50 mmol) in THF (30 mL) and H_2O (10 mL) was added LiOH (467 mg, 19.5 mmol). The mixture was stirred at room temperature for 6 h, and was then concentrated in vacuo to remove THF. The residue was adjusted to pH = 2–3 with 2 M aqueous HCl solution. The resulting precipitate was collected by filtration and washed with H_2O (100 mL) to give 3-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]oxetane-3-carboxylic acid, which was used in the subsequent step without further purification. MS = 448.3 $[M+H]^+$.

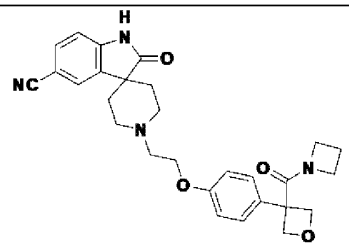
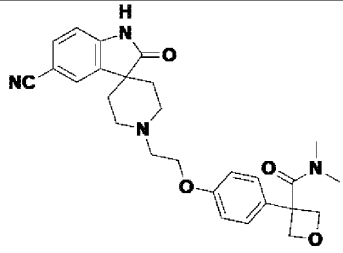
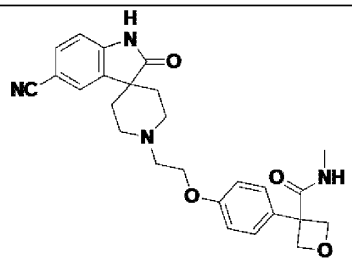
Step 8: 1'-(2-{4-[3-(3-fluoroazetidine-1-carbonyl)oxetan-3-yl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (Compound 252)



[1166] To a solution of 3-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]oxetane-3-carboxylic acid (100 mg, 0.223 mmol) and 3-fluoroazetidine hydrochloride (125 mg, 1.12 mmol) in DCM (2 mL) was added TEA (249 µL, 1.79 mmol). After stirring for 10 min, the reaction was cooled to 0 °C and T3P (199 µL, 0.670 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with DCM (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting solid was triturated with MeCN to give 1'-(2-{4-[3-(3-fluoroazetidine-1-carbonyl)oxetan-3-yl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (**Compound 252**). ^1H NMR (400 MHz, DMSO-d_6): δ 10.86 (s, 1H), 7.95 (s, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 8.0 Hz, 1H), 5.35–5.22 (m, 1H), 5.10–5.06 (m, 2H), 4.72–4.67 (m, 2H), 4.31–4.22 (m, 1H), 4.15 (s, 2H), 4.00–3.92 (m, 2H), 3.66–3.64 (m, 1H), 2.93–2.87 (m, 4H), 2.78–2.72 (m, 2H), 1.78–1.75 (m, 4H). MS = 505.2 $[M+H]^+$.

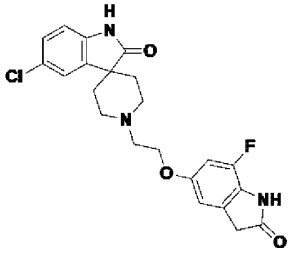
[1167] The following compounds in Table 37 were prepared according to procedures similar to those described for **Compound 252** using the appropriate starting materials.

Table 37.

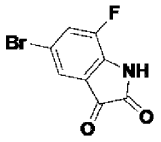
#	Structure	Name	Exact Mass $[M+H]^+$
253		1'-(2-{4-[3-(azetidine-1-carbonyl)oxetan-3-yl]phenoxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 487.2 Found 487.2
254		3-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-N,N-dimethyloxetane-3-carboxamide	Calc'd 475.2 Found 475.3
255		3-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-N-methyloxetane-3-carboxamide	Calc'd 461.2 Found 461.3

Example 45

5-chloro-1'-{2-[(7-fluoro-2-oxo-2,3-dihydro-1H-indol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 256)

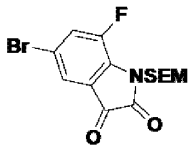


Step 1: 5-bromo-7-fluoro-2,3-dihydro-1H-indole-2,3-dione



[1168] A mixture of 7-fluoro-2,3-dihydro-1H-indole-2,3-dione (5.00 g, 30.3 mmol) and NBS (7.01 g, 39.4 mmol) in DMF (35 mL) was stirred at 80 °C for 2 h. After cooling to room temperature, the mixture was poured into H_2O (150 mL) and filtered to collect the solid. The filter cake was washed with H_2O (3 x 50 mL). The crude product was triturated with MTBE and dried in vacuo to give 5-bromo-7-fluoro-2,3-dihydro-1H-indole-2,3-dione, which was used in the subsequent step without further purification. MS = 243.9 / 245.9 $[M+H]^+$.

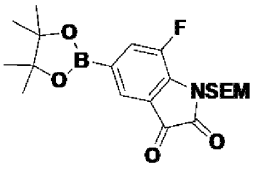
Step 2: 5-bromo-7-fluoro-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-indole-2,3-dione



[1169] To a 0 °C solution of 5-bromo-7-fluoro-2,3-dihydro-1H-indole-2,3-dione (5.00 g, 20.5 mmol) in DMA (50 mL) under N_2 atmosphere was added NaH (983 mg, 60 wt% in mineral oil, 24.6 mmol). The mixture was allowed to warm to room temperature and stirred for 30 min. After cooling to 0 °C, 2-(trimethylsilyl)ethoxymethyl chloride (4.71 mL, 26.6 mmol) was added. The mixture was warmed to room temperature and stirred for another 2 h. The mixture was quenched with saturated aqueous NH_4Cl solution (200 mL), and the mixture was extracted with EtOAc (3 x 70 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 80 g cartridge, 0–15%

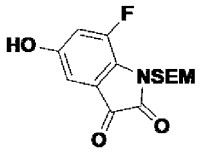
EtOAc:petroleum ether) to give 5-bromo-7-fluoro-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-indole-2,3-dione. MS = 391.1 / 393.1 $[M+NH_4]^+$.

Step 3: 7-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-indole-2,3-dione



[1170] A mixture of 5-bromo-7-fluoro-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-indole-2,3-dione (7.00 g, 18.7 mmol), bis(pinacolato)diboron (5.70 g, 22.4 mmol), KOAc (4.59 g, 46.8 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (1.22 g, 1.50 mmol) in 1,4-dioxane (70 mL) was stirred at 95 °C for 16 h under N_2 atmosphere. After cooling to room temperature, the mixture was poured into H_2O (200 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (80 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 120 g cartridge, 0–8% EtOAc:petroleum ether) to give 7-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-indole-2,3-dione. MS = 439.3 $[M+NH_4]^+$.

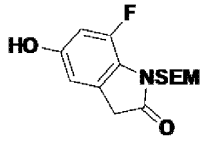
Step 4: 7-fluoro-5-hydroxy-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-indole-2,3-dione



[1171] To a 0 °C mixture of 7-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-indole-2,3-dione (7.80 g, 18.5 mmol) in acetone (70 mL) and H_2O (70 mL) was added Oxone (17.1 g, 27.8 mmol) portionwise. The mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was poured into saturated Na_2SO_3 solution (200 mL) and extracted with EtOAc (2 x 80 mL). The combined organic layers were washed with brine (60 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude residue was purified by normal phase silica gel chromatography (Biotage 80 g cartridge, 0–25%

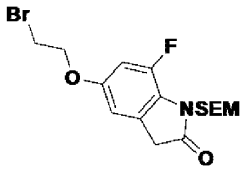
EtOAc:petroleum ether) to give 7-fluoro-5-hydroxy-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-indole-2,3-dione.

Step 5: 7-fluoro-5-hydroxy-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-indol-2-one



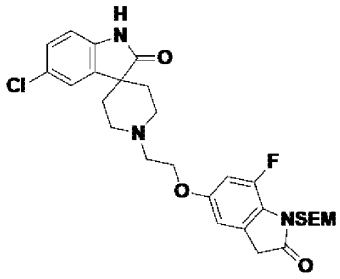
[1172] To a solution of 7-fluoro-5-hydroxy-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-indole-2,3-dione (4.30 g, 13.8 mmol) in DMSO (43 mL) was added $N_2H_4 \bullet H_2O$ (11.8 mL, 207 mmol). The mixture was stirred at 120 °C for 3 h. The mixture was diluted with H_2O (150 mL) and extracted with EtOAc (2 x 80 mL). The combined organic layers were washed with brine (60 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 40 g cartridge, 0–20% EtOAc:petroleum ether) to give 7-fluoro-5-hydroxy-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-indol-2-one. MS = 296.1 $[M–H]^-$.

Step 6: 5-(2-bromoethoxy)-7-fluoro-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-indol-2-one



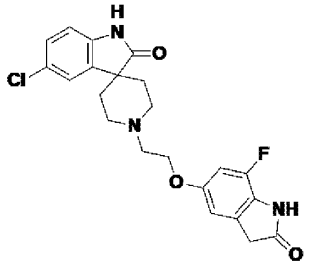
[1173] To a 0 °C mixture of 7-fluoro-5-hydroxy-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-indol-2-one (500 mg, 1.68 mmol), 2-bromoethanol (477 µL, 6.73 mmol), and PPh_3 (882 mg, 3.36 mmol) in THF (10 mL) was added DIAD (654 µL, 3.36 mmol). The mixture was allowed to warm to room temperature and stirred for 16 h. The mixture was diluted with EtOAc (25 mL) and H_2O (10 mL). The organic layer was separated, and washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 0–10% EtOAc:petroleum ether) to give 5-(2-bromoethoxy)-7-fluoro-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-indol-2-one.

Step 7: 5-chloro-1'-{2-[(7-fluoro-2-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-indol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one



[1174] A mixture of 5-(2-bromoethoxy)-7-fluoro-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-indol-2-one (170 mg, 0.420 mmol), 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 79.6 mg, 0.291 mmol), and $NaHCO_3$ (106 mg, 1.26 mmol) in MeCN (2 mL) was stirred at 80 °C for 16 h. After cooling to room temperature, the mixture was diluted with EtOAc (25 mL) and H_2O (10 mL). The organic layer was separated, washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–100% EtOAc:petroleum ether) to give 5-chloro-1'-{2-[(7-fluoro-2-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-indol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one. MS = 560.2 $[M+H]^+$.

Step 8: 5-chloro-1'-{2-[(7-fluoro-2-oxo-2,3-dihydro-1H-indol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 256)

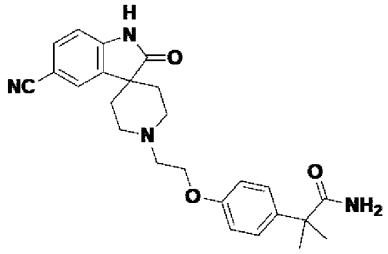


[1175] A solution of 5-chloro-1'-{2-[(7-fluoro-2-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-indol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (80.0 mg, 0.143 mmol) in 4.0 M HCl in 1,4-dioxane (2.0 mL, 8.0 mmol) was stirred at room temperature for 1 h. The mixture was concentrated in vacuo, and then $NH_3 \cdot H_2O$ (0.5 mL) was added dropwise. The mixture was stirred at room temperature for 30 min, and then diluted with H_2O (5 mL). The mixture was extracted with EtOAc (2 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC

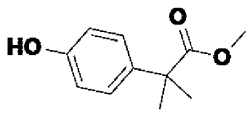
(Phenomenex C_{18} column, 20–50% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-{2-[(7-fluoro-2-oxo-2,3-dihydro-1H-indol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 256**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.67 (s, 1H), 10.51 (s, 1H), 7.53 (s, 1H), 7.26 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.82–6.80 (m, 2H), 4.11 (t, J = 5.6 Hz, 2H), 3.54 (s, 2H), 2.93–2.86 (m, 2H), 2.85–2.82 (m, 2H), 2.73–2.70 (m, 2H), 1.81–1.73 (m, 4H). MS = 430.2 $[M+H]^+$.

Example 46

2-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-2-methylpropanamide (Compound 257)

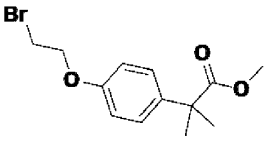


Step 1: methyl 2-(4-hydroxyphenyl)-2-methylpropanoate



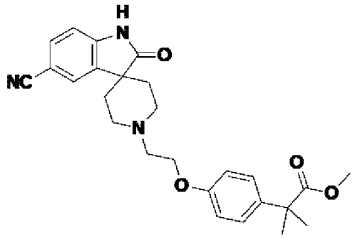
[1176] To a 0 °C solution of 2-(4-hydroxyphenyl)-2-methylpropanoic acid (900 mg, 4.99 mmol) in MeOH (18 mL) was added $SOCl_2$ (471 µL, 6.49 mmol). The mixture was stirred at 70 °C for 2 h. After cooling to room temperature, the mixture was concentrated in vacuo. The residue was diluted with H_2O (30 mL), extracted with EtOAc (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated to give methyl 2-(4-hydroxyphenyl)-2-methylpropanoate, which was used in the subsequent step without further purification. MS = 193.1 $[M–H]^–$.

Step 2: methyl 2-[4-(2-bromoethoxy)phenyl]-2-methylpropanoate



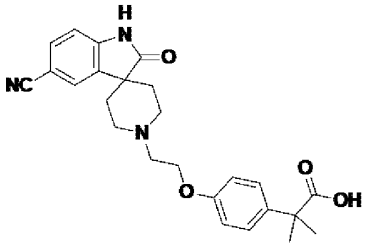
[1177] To a solution of methyl 2-(4-hydroxyphenyl)-2-methylpropanoate (820 mg, 4.22 mmol) and 1,2-dibromoethane (12.7 mL, 169 mmol) in MeCN (16 mL) was added K_2CO_3 (2.92 g, 21.1 mmol). After stirring at 80 °C for 16 h, the mixture was concentrated in vaccum. The residue was diluted with H_2O (30 mL), extracted with EtOAc (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 40 g cartridge, 0–20% EtOAc:petroleum ether) to give methyl 2-[4-(2-bromoethoxy)phenyl]-2-methylpropanoate. MS = 301.0 $[M+H]^+$.

Step 3: methyl 2-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-2-methylpropanoate



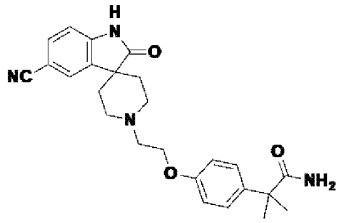
[1178] To a solution of methyl 2-[4-(2-bromoethoxy)phenyl]-2-methylpropanoate (300 mg, 0.996 mmol) and 2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (**Intermediate B-9**, 272 mg, 1.03 mmol, HCl salt) in MeCN (3 mL) was added $NaHCO_3$ (251 mg, 2.99 mmol). The mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the residue was diluted with H_2O (50 mL), extracted with EtOAc (2 x 30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–75% EtOAc:petroleum ether) to give methyl 2-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-2-methylpropanoate. MS = 448.2 $[M+H]^+$.

Step 4: 2-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-2-methylpropanoic acid



[1179] To a solution of methyl 2-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-2-methylpropanoate (120 mg, 0.268 mmol) in THF (2 mL) was added a solution of NaOH (26.8 mg, 0.670 mmol) in H_2O (1 mL). The mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with H_2O (5 mL) and then adjusted pH = 3–4 with 4.0 M aqueous HCl solution. The residue was extracted with EtOAc (2 x 20 mL) and washed with brine (10 mL). The organic combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give 2-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-2-methylpropanoic acid, which was used in the subsequent step without further purification. MS = 434.2 $[M+H]^+$.

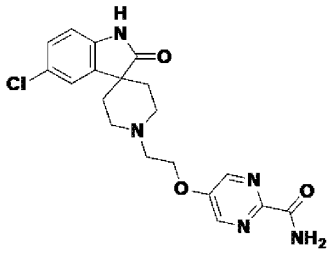
Step 5: 2-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-2-methylpropanamide (Compound 257)



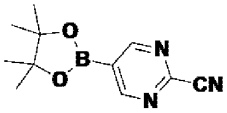
[1180] To a solution of 2-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-2-methylpropanoic acid (80.0 mg, 0.186 mmol) and NH_4Cl (11.9 mg, 0.221 mmol) in THF (0.5 mL) was added DIEA (77.2 µL, 0.443 mmol) and HATU (84.2 mg, 0.221 mmol). The mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters Xbridge Prep OBD C_{18} column, 20–50% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 2-[4-(2-{5-cyano-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)phenyl]-2-methylpropanamide (**Compound 257**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.83 (br s, J = 1.2 Hz, 1H) 7.93 (d, J = 1.2 Hz, 1H) 7.65 (dd, J = 8.0, 1.5 Hz, 1H) 7.19–7.25 (m, 2H) 6.96 (d, J = 8.0 Hz, 1H) 6.88 (d, J = 8.8 Hz, 2H), 6.78 (br d, J = 6.4 Hz, 2H), 4.09 (t, J = 6.0 Hz, 2H), 2.90–2.82 (m, 4H), 2.73–2.71 (m, 2H), 1.84–1.66 (m, 4H), 1.38 (s, 6H). MS = 433.2 $[M+H]^+$.

Example 47

5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)pyrimidine-2-carboxamide (Compound 258)

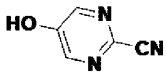


Step 1: 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine-2-carbonitrile



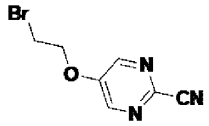
[1181] To a mixture of 5-bromopyrimidine-2-carbonitrile (1.00 g, 5.43 mmol) and bis(pinacolato)diboron (1.56 g, 6.52 mmol) in dioxane (10 mL) under N_2 atmosphere was added KOAc (1.07 g, 10.9 mmol) and $Pd(dppf)Cl_2$ (199 mg, 0.272 mmol). The mixture was degassed and purged with N_2 (3x), and then stirred at 80 °C for 12 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo. The residue was diluted with H_2O (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–35% EtOAc:petroleum ether) to give 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine-2-carbonitrile. MS = 232.2 $[M+H]^+$.

Step 2: 5-hydroxypyrimidine-2-carbonitrile



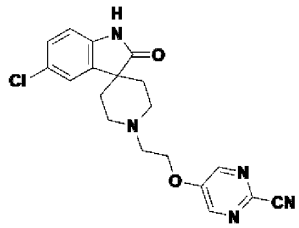
[1182] To a 0 °C solution of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine-2-carbonitrile (15.0 g, 64.9 mmol) in acetone (100 mL) and H_2O (100 mL) was added Oxone (47.9 g, 77.9 mmol). The mixture was stirred at room temperature for 1 h and was then quenched with saturated Na_2SO_3 (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 100 g cartridge, 0–65% EtOAc:petroleum ether) to give 5-hydroxypyrimidine-2-carbonitrile. MS = 122.0 $[M+H]^+$.

Step 3: 5-(2-bromoethoxy)pyrimidine-2-carbonitrile



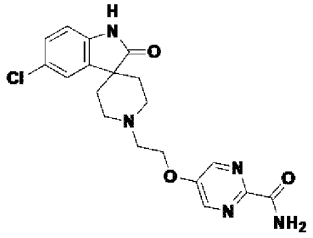
[1183] To a mixture of 5-hydroxypyrimidine-2-carbonitrile (300 mg, 2.48 mmol) and 1,2-dibromoethane (7.48 mL, 99.1 mmol) in MeCN (6 mL) was added K_2CO_3 (1.03 g, 7.43 mmol). The mixture was stirred at 60 °C for 12 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo to remove MeCN. The residue was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 4 g cartridge, 0–60% EtOAc:petroleum ether) to give 5-(2-bromoethoxy)pyrimidine-2-carbonitrile. MS = 228.1 / 230.1 $[M+H]^+$.

Step 4: 5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)pyrimidine-2-carbonitrile



[1184] To a mixture of 5-(2-bromoethoxy)pyrimidine-2-carbonitrile (165 mg, 0.724 mmol) and 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 206 mg, 0.868 mmol,) in MeCN (2 ml) was added $NaHCO_3$ (122 mg, 1.45 mmol). The mixture was stirred at 80 °C for 12 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo to remove MeCN. The residue was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated 5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)pyrimidine-2-carbonitrile, which was used in the subsequent step without further purification. MS = 384.2 $[M+H]^+$.

Step 5: 5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)pyrimidine-2-carboxamide (Compound 258)

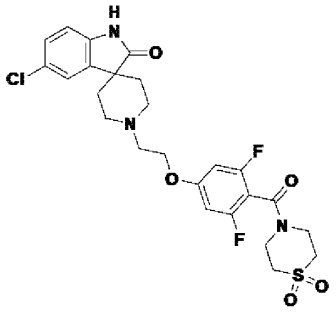


[1185] To a 0 °C mixture of 5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)pyrimidine-2-carbonitrile (160 mg, 0.417 mmol) and K_2CO_3 (115 mg, 0.834 mmol) in DMSO (2 mL) was added H_2O_2 in H_2O (120 µL, 30 wt% 1.25 mmol) dropwise. The mixture was stirred at room temperature for 2 h. The reaction mixture was cooled to 0 °C, quenched with saturated aqueous Na_2SO_3 solution (5 mL), diluted with H_2O (5 mL), and then extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters Xbridge Prep OBD C_{18} column, 15–40% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)pyrimidine-2-carboxamide (**Compound 258**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.50 (s, 1H), 8.68 (s, 2H), 8.05 (s, 1H), 7.65 (s, 1H), 7.52 (d, J = 2.00 Hz, 1H), 7.25 (dd, J = 10.40, 6.00 Hz, 1H), 6.87 (d, J = 8.40 Hz, 1H), 4.41 (t, J = 5.60 Hz, 2H), 2.99–2.88 (m, 4H), 2.76–2.70 (m, 2H), 1.84–1.68 (m, 4H). MS = 402.2 $[M+H]^+$.

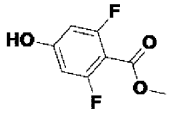
Example 48

4-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,6-difluorobenzoyl]-1λ⁶-thiomorpholine-1,1-dione

(Compound 259)

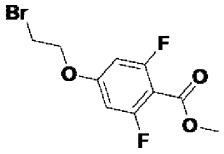


Step 1: methyl 2,6-difluoro-4-hydroxybenzoate



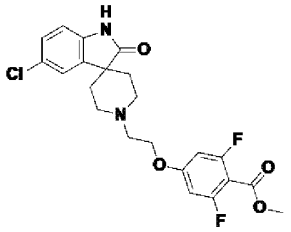
[1186] To a 0 °C solution of 2,6-difluoro-4-hydroxybenzoic acid (4.50 g, 25.9 mmol) in MeOH (45 mL) and MTBE (45 mL) was added 2.0 M diazomethyl(trimethyl)silane in DCM (14.2 mL, 28.4 mmol) dropwise. The mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was concentrated in vacuo to provide methyl 2,6-difluoro-4-hydroxybenzoate, which was used in the subsequent step without further purification. MS = 187.1 $[M–H]^+$.

Step 2: methyl 4-(2-bromoethoxy)-2,6-difluorobenzoate



[1187] To a solution of methyl 2,6-difluoro-4-hydroxybenzoate (4.38 g, 23.3 mmol) in MeCN (15 mL) was added K_2CO_3 (16.1 g, 116 mmol) and 1,2-dibromoethane (70.3 mL, 931 mmol). The mixture was heated to 80 °C and stirred for 16 h. After cooling room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo to provide methyl 4-(2-bromoethoxy)-2,6-difluorobenzoate, which was used in the subsequent step without further purification. MS = 295.2 / 296.8 $[M+H]^+$.

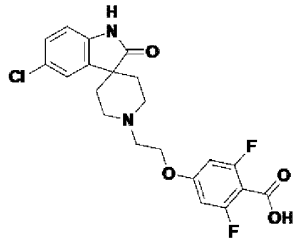
Step 3: methyl 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,6-difluorobenzoate



[1188] To a solution of methyl 4-(2-bromoethoxy)-2,6-difluorobenzoate (3.00 g, 10.2 mmol) in MeCN (60 mL) was added $NaHCO_3$ (2.56 g, 30.5 mmol) and 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 2.41 g, 8.82 mmol, HCl salt). The mixture was heated to 80 °C and stirred for 16 h. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo. The filtrate was diluted with H_2O and then extracted with a 10:1

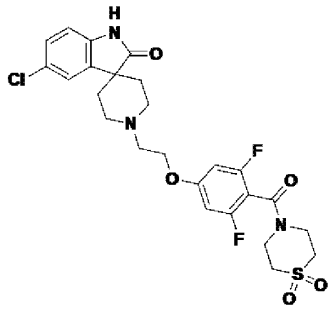
solution of DCM:MeOH (3 x 40 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex Luna C_{18} column, 20–50% MeCN: 10 mM TFA in H_2O) to give methyl 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,6-difluorobenzoate. MS = 451.1 $[M+H]^+$.

Step 4: 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,6-difluorobenzoic acid



[1189] To a solution of methyl 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,6-difluorobenzoate (1.60 g, 3.55 mmol) in THF (32 mL) and H_2O (64 mL) was added $LiOH \cdot H_2O$ (596 mg, 14.2 mmol). The mixture was stirred at room temperature for 16 h, and then was concentrated in vacuo. The residue was diluted with EtOAc (50 mL) and H_2O (10 mL) and was adjusted to pH = 5–6 with dropwise addition of 1.0 M aqueous HCl. The organic layer was separated, and aqueous phase was extracted with EtOAc (2 x 40 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,6-difluorobenzoic acid, which was used in the subsequent step without further purification. MS = 437.0 $[M+H]^+$.

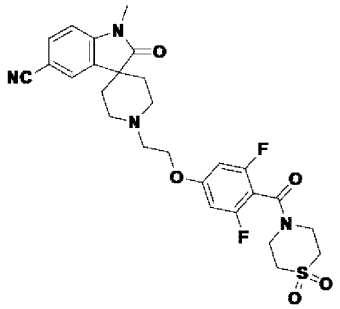
Step 5: 4-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,6-difluorobenzoyl]-1λ⁶-thiomorpholine-1,1-dione (Compound 259)



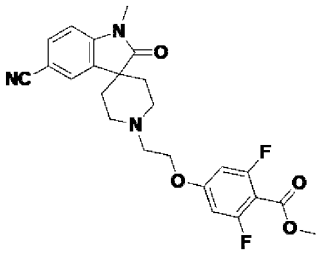
[1190] To a 0 °C solution of 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,6-difluorobenzoic acid (1.00 g, 2.29 mmol) in DMF (5 mL) was added 1-methylimidazole (0.547 mL, 6.87 mmol) and 1λ⁶-thiomorpholine-1,1-dione (464 mg, 3.43 mmol). After stirring for 10 min, [chloro(dimethylamino)methylene]-dimethyl-ammonium hexafluorophosphate (963 mg, 3.43 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was poured into the H_2O (30 mL) and then extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Kromasil C_{18} column, 20–60% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 4-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,6-difluorobenzoyl]-1λ⁶-thiomorpholine-1,1-dione (**Compound 259**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 1H), 7.51 (d, J = 1.6 Hz, 1H), 7.24 (d, J = 8.4, 2.0 Hz, 1H), 6.94 (d, J = 9.6 Hz, 2H), 6.85 (d, J = 8.4 Hz, 1H), 4.22 (t, J = 5.2 Hz, 2H), 4.11–4.05 (m, 2H), 3.79–3.69 (m, 2H), 3.29–3.28 (m, 2H), 3.11–3.10 (m, 2H), 2.91–2.84 (m, 4H), 2.68–2.67 (m, 2H), 1.78–1.70 (m, 4H). MS = 554.2 $[M+H]^+$.

Example 49

1'-{2-[4-(1,1-dioxo-1λ⁶-thiomorpholine-4-carbonyl)-3,5-difluorophenoxy]ethyl}-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (Compound 260)

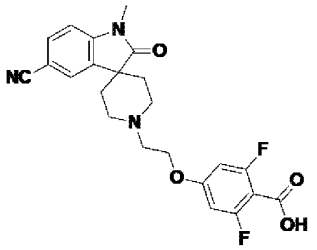


Step 1: methyl 4-(2-{5-cyano-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,6-difluorobenzoate



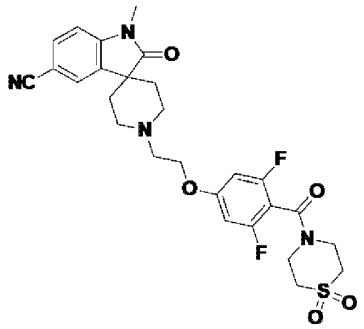
[1191] To a solution of methyl 4-(2-bromoethoxy)-2,6-difluorobenzoate (**Example 48**: Step 2, 300 mg, 1.02 mmol) in MeCN (4 mL) was added $NaHCO_3$ (256 mg, 3.05 mmol) and 1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (**Intermediate B-15**, 245 mg, 1.02 mmol). The mixture was heated to 80 °C and stirred for 16 h. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo. The crude residue was purified by preparative TLC (SiO_2, 10:1 DCM:MeOH) to give methyl 4-(2-{5-cyano-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,6-difluorobenzoate. MS = 456.2 $[M+H]^+$.

Step 2: 4-(2-{5-cyano-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,6-difluorobenzoic acid



[1192] To a solution of methyl 4-(2-{5-cyano-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,6-difluorobenzoate (290 mg, 0.637 mmol) in THF (3.6 mL) and H_2O (2.0 mL) was added $LiOH \cdot H_2O$ (53.4 mg, 1.42 mmol). The mixture was stirred at room temperature for 16 h. The reaction mixture was poured into H_2O (10 mL) and adjusted to pH = 4–6 via the dropwise addition of 1.0 M aqueous HCl. The mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give 4-(2-{5-cyano-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,6-difluorobenzoic acid, which was used in the subsequent step without further purification. MS = 442.2 $[M+H]^+$.

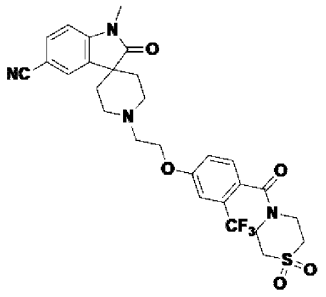
Step 3: 1'-{2-[4-(1,1-dioxo-1λ⁶-thiomorpholine-4-carbonyl)-3,5-difluorophenoxy]ethyl}-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (Compound 260)



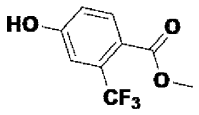
[1193] To a solution of 1λ⁶-thiomorpholine-1,1-dione (62.2 mg, 0.362 mmol, HCl salt) and 4-(2-{5-cyano-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2,6-difluorobenzoic acid (80.0 mg, 0.181 mmol) in DMF (2 mL) was added 1-methylimidazole (72.2 µL, 0.906 mmol). After stirring for 10 min, [chloro(dimethylamino)methylene]-dimethyl-ammonium hexafluorophosphate (102 mg, 0.363 mmol) was added and the mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with H_2O (1 mL), solids were removed by filtration, and the filtrate was concentrated in vacuo. The residue was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex C_{18} column, 15–45% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 1'-{2-[4-(1,1-dioxo-1λ⁶-thiomorpholine-4-carbonyl)-3,5-difluorophenoxy]ethyl}-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (**Compound 260**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99 (s, 1H), 7.80 (dd, J = 8.0, 1.6, 1H), 7.20 (d, J = 8.4 Hz, 1H), 6.94 (d, J = 10 Hz, 2H), 4.22 (t, J = 5.4 Hz, 2H), 4.08–4.05 (m, 2H), 3.74–3.71 (m, 2H), 3.35–3.27 (m, 2H), 3.14 (s, 3H), 3.09 (br s, 2H), 2.90–2.87 (m, 4H), 2.85–2.74 (m, 2H), 1.78 –1.74 (m, 4H). MS = 559.2 $[M+H]^+$.

Example 50

1'-{2-[4-(1,1-dioxo-1λ⁶-thiomorpholine-4-carbonyl)-3-(trifluoromethyl)phenoxy]ethyl}-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (Compound 261)

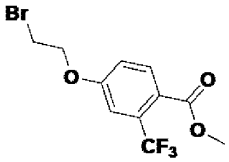


Step 1: methyl 4-hydroxy-2-(trifluoromethyl)benzoate



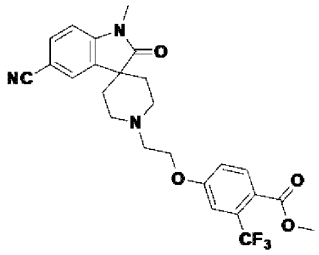
[1194] To a 0 °C solution of 4 4-hydroxy-2-(trifluoromethyl)benzoic acid (3.30 g, 16.0 mmol) in MeOH (50 mL) was added $SOCl_2$ (11.0 mL,152 mmol) dropwise. The mixture was heated to 50 °C and stirred for 12 h. The mixture was cooled to 0 °C and quenched with saturated NH_4Cl aqueous solution (100 mL). The aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 40 g cartridge, 0–50% EtOAc:petroleum ether) to give methyl 4-hydroxy-2-(trifluoromethyl)benzoate. MS = 221.1 $[M+H]^+$

Step 2: methyl 4-(2-bromoethoxy)-2-(trifluoromethyl)benzoate



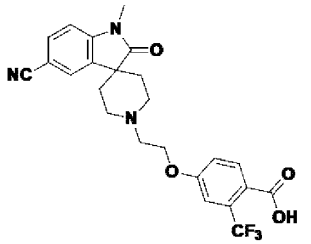
[1195] To a solution of methyl 4-hydroxy-2-(trifluoromethyl)benzoate (2.50 g, 11.4 mmol) and 1,2-dibromoethane (34.3 mL, 454 mmol) in MeCN (35 mL) was added K_2CO_3 (7.85 g, 56.8 mmol). The mixture was heated to 65 °C and then stirred for 12 h. After cooling to room temperature, the mixture was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 40 g cartridge, 0–50% EtOAc:petroleum ether) to give methyl 4-(2-bromoethoxy)-2-(trifluoromethyl)benzoate. MS = 327.1 / 329.1 $[M+H]^+$.

Step 3: methyl 4-(2-{5-cyano-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(trifluoromethyl)benzoate



[1196] To a solution of 1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (**Intermediate B-15**, 154 mg, 0.556 mmol, HCl salt) and methyl 4-(2-bromoethoxy)-2-(trifluoromethyl)benzoate (200 mg, 0.611 mmol) in MeCN (8 mL) was added $NaHCO_3$ (140 mg, 1.67 mmol). The mixture was heated to 80° C and stirred for 12 h. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–50% EtOAc:petroleum ether) to give methyl 4-(2-{5-cyano-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(trifluoromethyl)benzoate. MS = 488.3 $[M+H]^+$

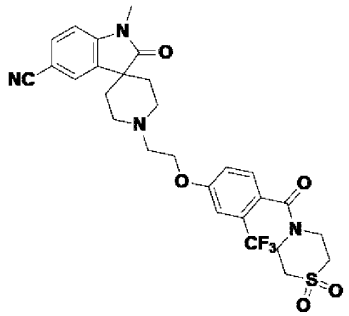
Step 4: 4-(2-{5-cyano-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(trifluoromethyl)benzoic acid



[1197] To a solution of methyl 4-(2-{5-cyano-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(trifluoromethyl)benzoate (250 mg, 0.513 mmol) in MeOH (5 mL) and H_2O (5 mL) was added $LiOH \cdot H_2O$ (172 mg, 4.10 mmol). The mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo to remove MeOH, and the resulting aqueous phase was adjusted to pH = 4–6 via dropwise addition of 1.0 M aqueous HCl. The resulting solid was isolated by filtration, washed with MTBE, and dried in vacuo to give 4-(2-{5-cyano-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-

(trifluoromethyl)benzoic acid, which was taken to the subsequent step without further purification. MS = 474.2 $[M+H]^+$.

Step 5: 1'-{2-[4-(1,1-dioxo-1λ⁶-thiomorpholine-4-carbonyl)-3-(trifluoromethyl)phenoxy]ethyl}-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (Compound 261)



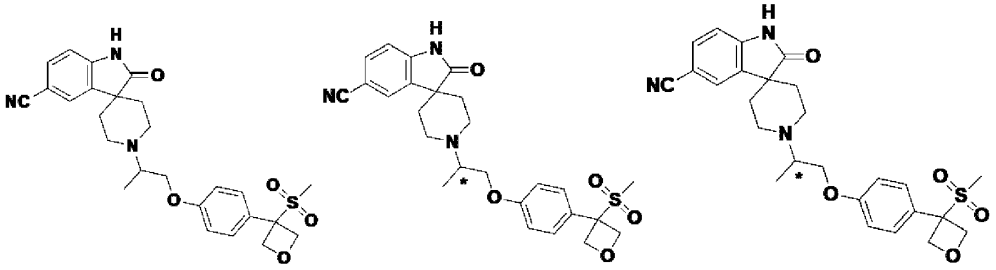
[1198] To a 0 °C solution of 4-(2-{5-cyano-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(trifluoromethyl)benzoic acid (100 mg, 0.211 mmol), 1λ⁶-thiomorpholine-1,1-dione (39.9 mg, 0.232 mmol, HCl salt) and DIEA (92.0 µL, 0.528 mmol) in DMF (2 mL) was added HATU (120 mg, 0.317 mmol). The mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was poured into H_2O (5 mL) and then extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters Xbridge Prep OBD C_{18} column, 15–45% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 1'-{2-[4-(1,1-dioxo-1λ⁶-thiomorpholine-4-carbonyl)-3-(trifluoromethyl)phenoxy]ethyl}-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (**Compound 261**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.00 (s, 1H), 7.80 (d, J = 9.6 Hz, 1H), 7.68 (d, J = 8.4, 1H), 7.38–7.35 (m, 2H), 7.21 (d, J = 8.0, 1H), 4.47 (br d, J = 13.2, 1H), 4.29–4.26 (m, 2H), 3.59–3.56 (m, 2H), 3.46–3.41 (m, 2H), 3.29–3.28 (m, 1H), 3.20–3.16 (m, 4H), 2.95–2.88 (m, 5H), 3.77–3.74 (m, 2H), 1.84–1.68 (m, 4H). MS = 591.3 $[M+H]^+$.

Example 51

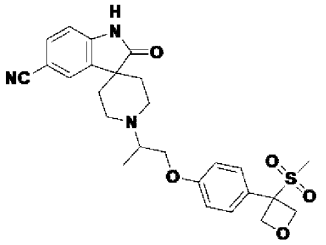
1'-{1-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (Compound 262),

***(S)* or *(R)*-1'-{1-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (Compound 263),**

and *(R)* or (*S*)-1'-{1-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (Compound 264)



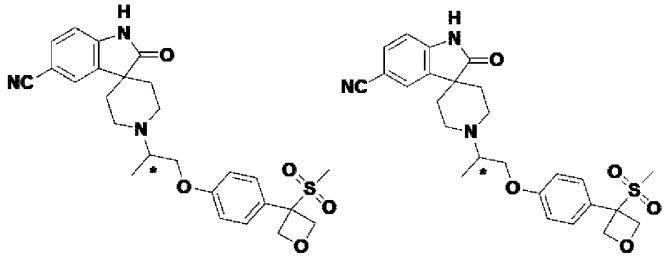
Step 1: 1'-{1-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (Compound 262)



[1199] A mixture of 1-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]propan-2-yl methanesulfonate (**Intermediate A-36**, 385 mg, 1.06 mmol), 2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (**Intermediate B-9**, 200 mg, 0.880 mmol), $NaHCO_3$ (296 mg, 3.52 mmol) and KI (292 mg, 1.76 mmol) in DMF (1 mL) was degassed and purged with N_2 (3x). The mixture was stirred at 90 °C for 15 h under N_2 atmosphere. After cooling to room temperature, the reaction mixture was quenched with H_2O (15 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex C_{18} column, 20–40% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 1'-{1-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (**Compound 262**). MS = 496.1 $[M+H]^+$.

Step 2: *(S)* or (*R*)-1'-{1-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (Compound 263),

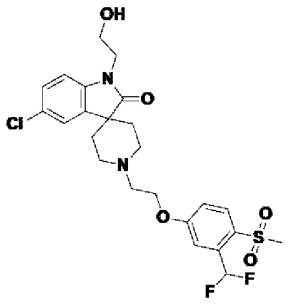
and *(R)* or (*S*)-1'-{1-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (Compound 264)



[1200] 1'-{1-[4-(3-methanesulfonyloxetan-3-yl)phenoxy]propan-2-yl}-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (110 mg, 0.222 mmol) was purified by preparative chiral SFC (Dailcel Chiralpak AD-3, 60% ethanol with 0.1% NH_4OH in CO_2). The first eluting enantiomer of the title compound, **Compound 263**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.86 (s, 1H), 7.87 (s, 1H), 7.68 (dd, J = 8.4, 1.6 Hz, 1H), 7.26 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.0 Hz, 1H), 5.21 (d, J = 7.6 Hz, 2H), 5.00 (d, J = 7.6 Hz, 2H), 4.50–4.20 (m, 1H), 4.01–3.98 (m, 1H), 3.14–3.09 (m, 1H), 3.03–3.01 (m, 2H), 2.89–2.84 (m, 4H), 2.79–2.74 (m, 1H), 1.81–1.68 (m, 4H), 1.16 (d, J = 7.2 Hz, 3H). MS = 496.1 $[M+H]^+$. The second eluting enantiomer of the title compound, **Compound 264**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.87 (s, 1H), 7.87 (s, 1H), 7.68 (dd, J = 8.0, 1.6 Hz, 1H), 7.26 (d, J = 8.8 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.0 Hz, 1H), 5.19 (d, J = 7.2 Hz, 2H), 5.00 (d, J = 7.6 Hz, 2H), 4.21–4.13 (m, 1H), 4.05–3.98 (m, 1H), 3.15–3.13 (m, 1H), 3.04 –3.03 (m, 2H), 2.89 –2.84 (m, 4H), 2.81–2.77 (m, 1H), 1.82–1.72 (m, 4H), 1.18 (d, J = 6.8 Hz, 3H). MS = 496.1 $[M+H]^+$.

Example 52

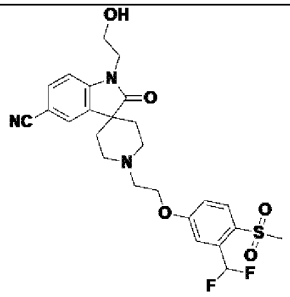
5-chloro-1'-{2-[3-(difluoromethyl)-4-methanesulfonylphenoxy]ethyl}-1-(2-hydroxyethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 265)



[1201] To a solution of 5-chloro-1'-{2-[3-(difluoromethyl)-4-methanesulfonylphenoxy]ethyl}-1-(2-hydroxyethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 197**, 100 mg, 0.206 mmol) in DMF (1 mL) was added K_2CO_3 (142 mg, 1.03 mmol) and 2-bromoethanol (155 mg, 1.24 mmol). The mixture was stirred at 80 °C for 12 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex C_{18} column, 30–65% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-{2-[3-(difluoromethyl)-4-methanesulfonylphenoxy]ethyl}-1-(2-hydroxyethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 265**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99 (d, J = 8.8 Hz, 1H), 7.59–7.52 (m, 2H), 7.33–7.30 (m, 3H), 7.09 (d, J = 8.4 Hz, 1H), 4.82 (t, J = 5.6 Hz, 1H), 4.32 (t, J = 5.6 Hz, 2H), 3.70 (t, J = 5.6 Hz, 2H), 3.59–3.52 (m, 2H), 3.26 (s, 3H), 2.99–2.86 (m, 4H), 2.77–2.69 (m, 2H), 1.76 (s, 4H). MS = 529.1 $[M+H]^+$.

[1202] The following compound in Table 38 was prepared according to procedures similar to those described for **Compound 265** using the appropriate starting materials.

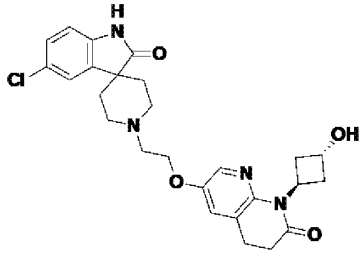
Table 38.

#	Structure	Name	Exact Mass $[M+H]^+$	Starting Material
266		1'-{2-[3-(difluoromethyl)-4-methanesulfonylphenoxy]ethyl}-1-(2-hydroxyethyl)-2-oxo-1,2-	Calc'd 520.2 Found 520.3	**Compound 100**

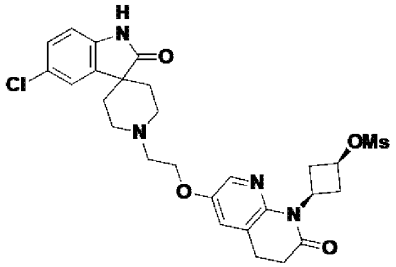
		dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile		

Example 53

5-chloro-1'-[2-({7-oxo-8-[(*trans*)-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 267)

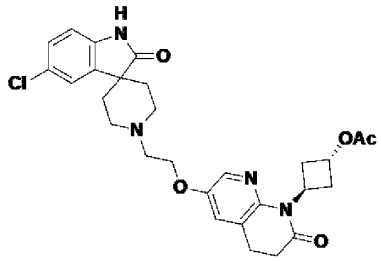


Step 1: (*cis*)-3-[6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridin-1-yl]cyclobutyl methanesulfonate



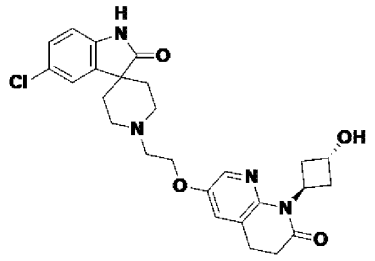
[1203] To a 0 °C solution of 5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 190**, 150 mg, 0.302 mmol) in DCM (5 mL) was added TEA (61.0 mg, 0.604 mmol) and methanesulfonic anhydride (79 mg, 0.453 mmol). The mixture was allowed to warm to room temperature and stirred for 12 h. The mixture was quenched with H_2O (10 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give (*cis*)-3-[6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridin-1-yl]cyclobutyl methanesulfonate, which was taken onto the next step without further purification. MS = 575.2 $[M+H]^+$.

Step 2: (*trans*)-3-[6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridin-1-yl]cyclobutyl acetate



[1204] To a solution of (*cis*)-3-[6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridin-1-yl]cyclobutyl methanesulfonate (200 mg, 0.348 mmol) in DMF (5 mL) was added KOAc (341 mg, 3.48 mmol). The mixture was heated to 100 °C and stirred for 12 h. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters Xbridge Prep OBD C_{18} column, 25–55% MeCN: 10 mM NH_4HCO_3 in H_2O) to give (*trans*)-3-[6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridin-1-yl]cyclobutyl acetate. MS = 539.3 $[M+H]^+$.

Step 3: 5-chloro-1'-[2-({7-oxo-8-[(*trans*)-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 267)



[1205] To a mixture of [(*trans*)-3-[6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridin-1-yl]cyclobutyl acetate (40.0 mg, 0.0742 mmol) in MeOH (2 mL) was added K_2CO_3 (20.5 mg, 0.148 mmol). The mixture was stirred at room temperature for 6 h. Solids were removed by filtration and the filtrate was concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters Xbridge BEH C_{18} column, 25–55% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-[2-({7-oxo-8-[(*trans*)-3-

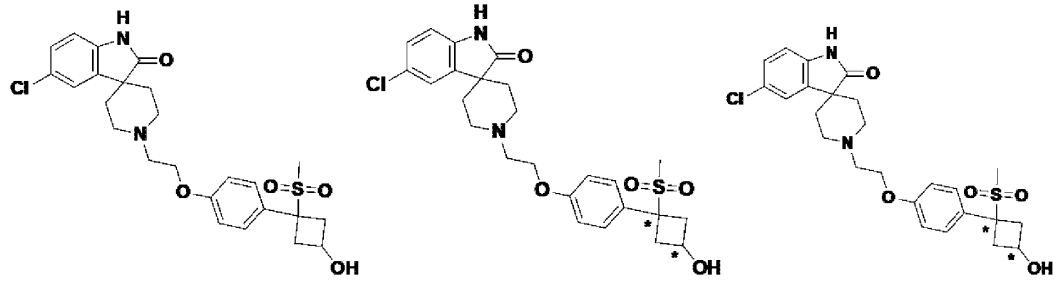
hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 267**). ^{1}HNMR (400 MHz, CD_3CN): δ 8.40 (br s, 1H), 7.90 (d, J = 2.8 Hz, 1H), 7.45 (d, J = 2.0 Hz, 1H), 7.24–7.16 (m, 2H), 6.87 (d, J = 8.4 Hz, 1H), 5.46 (q, J = 8.6 Hz, 1H), 4.47 (br s, 1H), 4.17 (t, J = 5.6 Hz, 2H), 3.04–2.84 (m, 7H), 2.83–2.77 (m, 2H), 2.77–2.67 (m, 2H), 2.56–2.48 (m, 2H), 2.27–2.18 (m, 2H), 1.91–1.82 (m, 2H), 1.79–1.70 (m, 2H). MS = 497.2 $[M+H]^+$.

Example 54

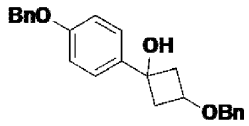
5-chloro-1'-{2-[4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 268)

5-chloro-1'-(2-{4-[(*cis*) or (*trans*)-3-hydroxy-1-methanesulfonylcyclobutyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 269)

5-chloro-1'-(2-{4-[(*trans*) or (*cis*)-3-hydroxy-1-methanesulfonylcyclobutyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 270)



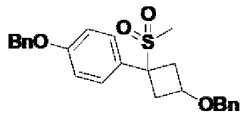
Step 1: 3-(benzyloxy)-1-[4-(benzyloxy)phenyl]cyclobutan-1-ol



[1206] To a –78 °C mixture of 1-(benzyloxy)-4-bromobenzene (34.0 g, 129 mmol) in THF (250 mL) was added 2.5 M *n*-BuLi in THF (62.0 mL, 155 mmol) dropwise. After stirring for 30 min, 3-benzyloxycyclobutanone (25.1 g, 142 mmol) in THF (50 mL) was added. The mixture was stirred at –78 °C for 1 h. The reaction mixture was allowed to warm to 0 °C and then quenched with H_2O (200 mL) and saturated aqueous NH_4Cl (200 mL). The mixture was extracted with EtOAc (3 x 250 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 330 g cartridge, 0–

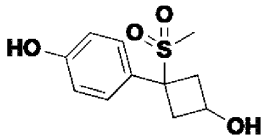
50% EtOAc:petroleum ether) to give 3-(benzyloxy)-1-[4-(benzyloxy)phenyl]cyclobutan-1-ol as a mixture of diastereomers. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.48–7.22 (m, 13H), 6.95–6.91 (m, 1H), 5.54 (s, 1H), 5.08 (s, 2H), 4.37 (s, 2H), 3.78–3.67 (m, 1H), 2.78–2.68 (m, 2H), 2.30–2.22 (m, 2H).

Step 2: 1-(benzyloxy)-4-[3-(benzyloxy)-1-methanesulfonylcyclobutyl]benzene



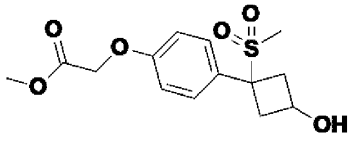
[1207] To a 0 °C solution of 3-(benzyloxy)-1-[4-(benzyloxy)phenyl]cyclobutan-1-ol (25.0 g, 69.4 mmol) and sodium methanesulfinate (35.4 g, 347 mmol) in DCM (300 mL) was added TFA (39.5 g, 347 mmol). The mixture was stirred at 0 °C for 2 h. The reaction mixture was then quenched with H_2O (300 mL) and extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine (3 x 300 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 12 g cartridge, 0–45% EtOAc:petroleum ether) to give 1-(benzyloxy)-4-[3-(benzyloxy)-1-methanesulfonylcyclobutyl]benzene. MS = 440.3 $[M+NH_4]^+$.

Step 3: 4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenol



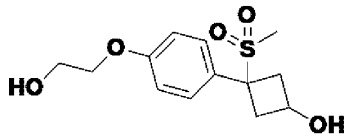
[1208] To a mixture of Pd/C (8.00 g, 10 wt%, 7.55 mmol) in MeOH (200 mL) was added 1-(benzyloxy)-4-[3-(benzyloxy)-1-methanesulfonylcyclobutyl]benzene (5.00 g, 11.8 mmol). The suspension was degassed under vacuum and purged with H_2 (3x). After allowing the mixture to stir at room temperature for 16 h under a H_2 atmosphere, the mixture was filtered through Celite. The filtrate was concentrated in vacuo to give 4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenol, which was taken to the next step without further purification. MS = 260.2 $[M+NH_4]^+$.

Step 4: methyl 2-[4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenoxy]acetate



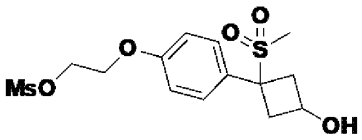
[1209] To a solution 4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenol (3.80 g, 15.7 mmol) and K_2CO_3 (3.25 g, 23.5 mmol) in DMF (30 mL) was added methyl 2-bromoacetate (2.88 g, 18.8 mmol). The mixture was stirred at room temperature for 16 h, and then quenched with H_20 (30 mL). The mixture was extracted with EtOAc (3 x 15 mL). The combined organic phase was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 10 g cartridge, 0–100% EtOAc:petroleum ether) to give methyl 2-[4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenoxy]acetate as a mixture of diastereomers. MS = 332.2 $[M+NH_4]^+$.

Step 5: 3-[4-(2-hydroxyethoxy)phenyl]-3-methanesulfonylcyclobutan-1-ol



[1210] To a 0 °C solution of methyl 2-[4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenoxy]acetate (500 mg, 1.59 mmol) in THF (25 mL) was added $LiAlH_4$ (151 mg, 3.98 mmol). The mixture was allowed to warm to room temperature and was stirred for 12 h. The mixture was quenched with saturated aqueous NH_4Cl (5 mL) and then extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 10 g cartridge, 0–100% EtOAc:petroleum ether) to give 3-[4-(2-hydroxyethoxy)phenyl]-3-methanesulfonylcyclobutan-1-ol. MS = 304.2 $[M+NH_4]^+$.

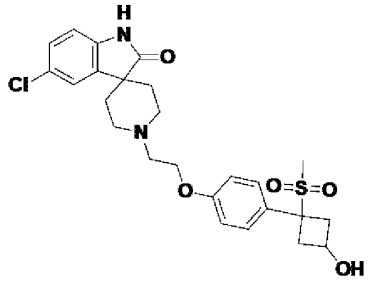
Step 6: 2-[4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenoxy]ethyl methanesulfonate



[1211] To a solution of 3-[4-(2-hydroxyethoxy)phenyl]-3-methanesulfonylcyclobutan-1-ol (220 mg, 0.77 mmol) in DCM (15 mL) was added TEA (233 mg, 2.30 mmol) and methanesulfonic anhydride (161 mg, 0.92 mmol). The resulting mixture was stirred at room temperature for 12 h. The mixture was quenched with H_2O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried with Na_2SO_4, filtered, and concentrated in

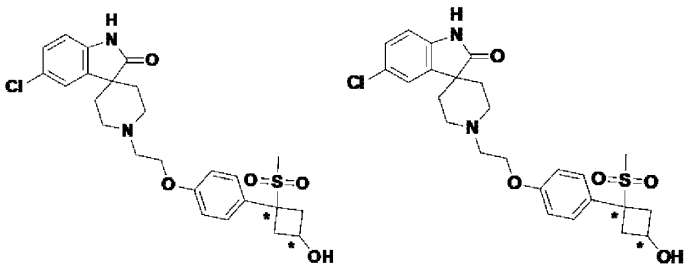
vacuo. The crude residue was purified by preparative TLC (SiO_2, 1:1 petroleum ether/EtOAc) to give 2-[4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenoxy]ethyl methanesulfonate as a mixture of diastereomers. MS = 382.1 $[M+NH_4]^+$.

Step 7: 5-chloro-1'-{2-[4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 268)



[1212] To a solution of 2-[4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenoxy]ethyl methanesulfonate (85.0 mg, 0.23 mmol) in MeCN (5 mL) was added $NaHCO_3$ (58.0 mg, 0.700 mmol) and 5-chloro-1'-(2-chloroethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 63.7 mg, 0.23 mmol, HCl salt). The mixture was stirred at 80 °C for 12 h. After allowing to cool to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters Xbridge BEH C_{18} column, 20–50% MeCN:10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-{2-[4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 268**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 7.51–7.47 (m, 2H), 7.24 (dd, J = 7.6, 2.0 Hz, 2H), 7.00 (t, J = 8.0 Hz, 2H), 6.84 (d, J = 8.4 Hz, 1H), 5.49–5.32 (m, 1H), 4.36–4.14 (m, 1H), 4.18–4.17 (m, 2H), 3.28–3.27 (m, 1H), 2.92–2.84 (m, 5H), 2.72–2.68 (m, 3H), 2.63–2.54 (m, 3H), 2.35–2.45 (m, 1H), 1.79–1.71 (m, 4H). MS = 505.2 $[M+H]^+$.

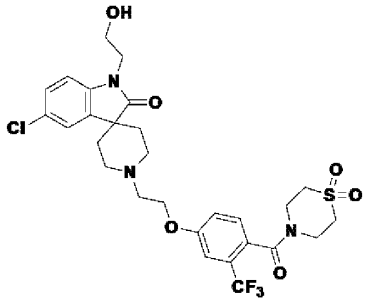
Step 8: 5-chloro-1'-(2-{4-[(*cis*) or (*trans*)-3-hydroxy-1-methanesulfonylcyclobutyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 269) and 5-chloro-1'-(2-{4-[(*trans*) or (*cis*)-3-hydroxy-1-methanesulfonylcyclobutyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 270)



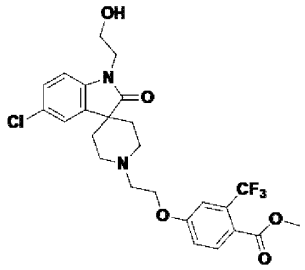
[1213] 5-chloro-1'-{2-[4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 268**) was separated by preparative chiral SFC (Chiralpak AD-3 column, 50% isopropanol with 0.1% NH_4OH in CO_2). The first eluting isomer of the title compound, 5-chloro-1'-(2-{4-[(*trans*) or (*cis*)-3-hydroxy-1-methanesulfonylcyclobutyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 270**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 1H), 7.55–7.44 (m, 3H), 7.23 (dd, J = 8.4, 2.0 Hz, 1H), 7.01 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.4 Hz, 1H), 5.49 (d, J = 6.4 Hz, 1H), 4.17 (t, J = 5.2 Hz, 2H), 3.90–3.75 (m, 1H), 2.98–2.79 (m, 6H), 2.76–2.66 (m, 4H), 2.54 (s, 3H), 1.86–1.64 (m, 4H). MS = 505.2 $[M+H]^+$. The second eluting isomer of the title compound, 5-chloro-1'-(2-{4-[(*cis*) or (*trans*)-3-hydroxy-1-methanesulfonylcyclobutyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 269**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 1H), 7.55–7.44 (m, 3H), 7.23 (dd, J = 8.4, 2.0 Hz, 1H), 7.01 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.4 Hz, 1H), 5.49 (d, J = 6.4 Hz, 1H), 4.17 (t, J = 5.2 Hz, 2H), 3.90–3.75 (m, 1H), 2.98–2.79 (m, 6H), 2.76–2.66 (m, 4H), 2.54 (s, 3H), 1.86–1.64 (m, 4H). MS = 505.2 $[M+H]^+$.

Example 55

4-(4-{2-[5-chloro-1-(2-hydroxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl]ethoxy}-2-(trifluoromethyl)benzoyl)-1λ⁶-thiomorpholine-1,1-dione (Compound 271)

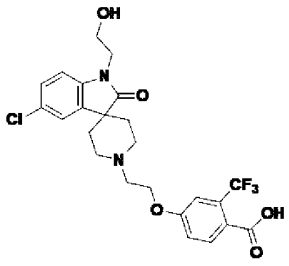


Step 1: methyl 4-{2-[5-chloro-1-(2-hydroxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl]ethoxy}-2-(trifluoromethyl)benzoate



[1214] To a room temperature solution of methyl 4-(2-bromoethoxy)-2-(trifluoromethyl)benzoate (**Example 50**, Step 2, 450 mg, 1.38 mmol) in MeCN (5 mL) was added $NaHCO_3$ (462 mg, 5.50 mmol) and 5-chloro-1-(2-hydroxyethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-11**, 524 mg, 1.65 mmol). The mixture was heated to 80 °C and stirred for 16 h. The mixture was allowed to cool to room temperature, then was diluted with H_2O (30 mL), and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 4 g cartridge, 0–35% EtOAc:petroleum ether) to give methyl 4-{2-[5-chloro-1-(2-hydroxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl]ethoxy}-2-(trifluoromethyl)benzoate. MS = 527.2. $[M+H]^+$.

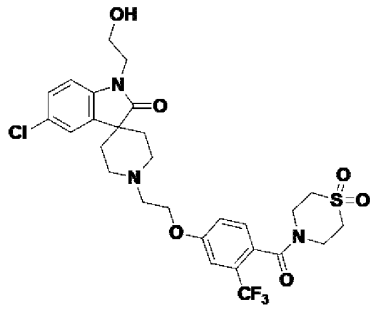
Step 2: 4-{2-[5-chloro-1-(2-hydroxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl]ethoxy}-2-(trifluoromethyl)benzoic acid



[1215] To a solution of methyl 4-{2-[5-chloro-1-(2-hydroxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl]ethoxy}-2-(trifluoromethyl)benzoate (750 mg, 1.42 mmol) in MeOH (5 mL) was added $LiOH \cdot H_2O$ (478 mg, 11.4 mmol) in H_2O (1 mL). The mixture was

stirred at 50 °C for 12 h, then was concentrated in vacuo. The resulting mixture was adjusted to pH = 4 via dropwise addition of 4.0 M aqueous HCl. The resulting solid was isolated by filtration and concentrated in vacuo to give 4-{2-[5-chloro-1-(2-hydroxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl]ethoxy}-2-(trifluoromethyl)benzoic acid, which was taken onto the subsequent step without further purification. MS = 513.1 $[M+H]^+$.

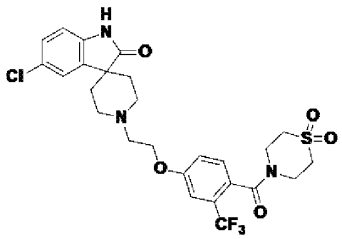
Step 3: 4-(4-{2-[5-chloro-1-(2-hydroxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl]ethoxy}-2-(trifluoromethyl)benzoyl)-1λ⁶-thiomorpholine-1,1-dione (Compound 271)



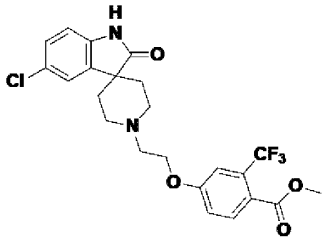
[1216] To a solution of 1λ⁶-thiomorpholine-1,1-dione (31 mg, 0.23 mmol) and 4-{2-[5-chloro-1-(2-hydroxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl]ethoxy}-2-(trifluoromethyl)benzoic acid (100 mg, 0.19 mmol) in DCM (2 mL) was added HOBt (8.0 mg, 0.058 mmol), EDCI (56.0 mg, 0.292.45 mmol) and TEA (79 mg, 0.78 mmol). The mixture was stirred at room temperature for 12 h, then was concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex C_{18} column, 20–55% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 4-(4-{2-[5-chloro-1-(2-hydroxyethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl]ethoxy}-2-(trifluoromethyl)benzoyl)-1λ⁶-thiomorpholine-1,1-dione (**Compound 271**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.68 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H), 7.42–7.26 (m, 3H), 7.10 (d, J = 8.4 Hz, 1H), 4.83 (t, J = 6.0 Hz, 1H), 4.48 (d, J = 13.6 Hz, 1H), 4.27 (t, J = 6.0 Hz, 2H), 3.69 (t, J = 6.0 Hz, 2H), 3.63–3.49 (m, 4H), 3.49–3.39 (m, 2H), 3.29–3.11 (m, 2H), 3.02–2.82 (m, 5H), 2.77–2.68 (m, 2H), 1.90–1.56 (m, 4H). MS = 630.2 $[M+H]^+$.

Example 56

4-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(trifluoromethyl)benzoyl]-1λ⁶-thiomorpholine-1,1-dione (Compound 272)

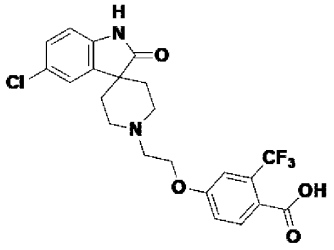


Step 1: Methyl 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(trifluoromethyl)benzoate



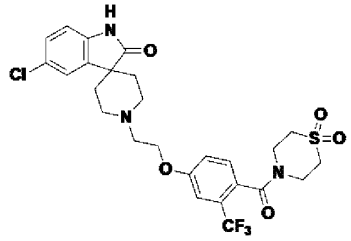
[1217] To a solution of methyl 4-(2-bromoethoxy)-2-(trifluoromethyl)benzoate (**Example 50**, Step 2, 1.0 g, 3.06 mmol) and 5-chlorospiro[indoline-3,4'-piperidine]-2-one (**Intermediate B-4**, 759 mg, 2.78 mmol, HCl salt) in MeCN (40 mL) was added $NaHCO_3$ (700 mg, 8.34 mmol). The mixture was heated to 80 °C and stirred for 12 h. The reaction mixture was allowed to cool to room temperature, then was filtered and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 0–100% EtOAc:petroleum ether) to give methyl 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(trifluoromethyl)benzoate. MS = 483.1 $[M+H]^+$.

Step 2: 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(trifluoromethyl)benzoic acid



[1218] To a solution of methyl 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(trifluoromethyl)benzoate (300 mg, 0.62 mmol) in MeOH (6 mL) and H_2O (6 mL) was added $LiOH \cdot H_2O$ (208 mg, 4.97 mmol). The mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo, and the aqueous phase was adjusted to pH = 4 via dropwise addition of 1.0 M aqueous HCl. The resulting solid was collected by filtration, washed with MTBE, and dried in vacuo to give 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(trifluoromethyl)benzoic acid which was taken to the next step without further purification. MS = 469.2 $[M+H]^+$.

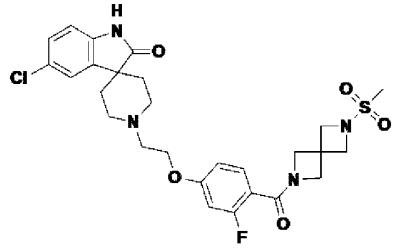
Step 3: 4-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(trifluoromethyl)benzoyl]-1λ⁶-thiomorpholine-1,1-dione (Compound 272)



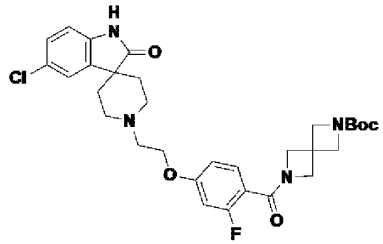
[1219] To a 0 °C solution of 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(trifluoromethyl)benzoic acid (100 mg, 0.21 mmol) and 1,4-thiazinane 1,1-dioxide (34.60 mg, 0.26 mmol) in DMF (2 mL) was added TEA (64.8 mg, 0.64 mmol), EDCI (61.3 mg, 0.32 mmol) and HOBt (5.8 mg, 0.043 mmol). The mixture was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was poured into the H_2O (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex C_{18} column, 10–55% MeCN: 10 mM NH_4HCO_3 in H_2O) to give 4-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-(trifluoromethyl)benzoyl]-1λ⁶-thiomorpholine-1,1-dione (**Compound 272**). ^1H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.50 (s, 1H), 7.38–7.35 (m, 2H), 7.24 (dd, J = 8.0, 2.4 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 4.49–4.45 (m, 1H), 4.27 (t, J = 5.6 Hz, 2H), 3.59–3.56 (m, 2H), 3.46–3.33 (m, 2H), 3.21–3.18 (m, 2H), 2.95–2.86 (m, 5H), 2.70–2.60 (m, 2H), 1.81–1.70 (m, 4H). MS = 586.2 $[M+H]^+$.

Example 57

5-chloro-1'-[2-(3-fluoro-4-{6-methanesulfonyl-2,6-diazaspiro[3.3]heptane-2-carbonyl}phenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 273)

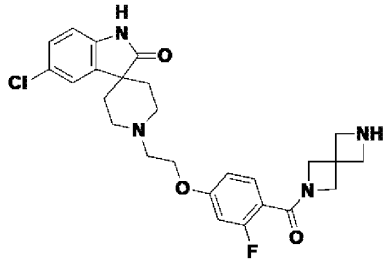


Step 1: *tert*-butyl 6-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzoyl]-2,6-diazaspiro[3.3]heptane-2-carboxylate



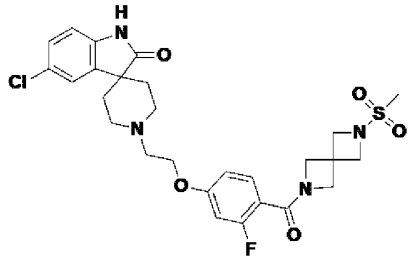
[1220] To a solution of 4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzoic acid (**Example 36**, Step 3, 1.15 g, 2.75 mmol) and *tert*-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate (950 mg, 3.29 mmol) in DMF (12 mL) was added TEA (1.11 g, 11.0 mmol), HOBt (74.2 mg, 0.549 mmol), then EDCI (1.05 g, 5.49 mmol). The mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with H_2O (30 mL) and then extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography (Biotage 20 g cartridge, 50–100% EtOAc:petroleum ether) to give tert-butyl 6-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzoyl]-2,6-diazaspiro[3.3]heptane-2-carboxylate. MS = 599.2 $[M+H]^+$.

Step 2: 5-chloro-1'-[2-(4-{2,6-diazaspiro[3.3]heptane-2-carbonyl}-3-fluorophenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one



[1221] To a solution of tert-butyl 6-[4-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-fluorobenzoyl]-2,6-diazaspiro[3.3]heptane-2-carboxylate (1.40 g, 2.34 mmol) in DCM (20 mL) was added TFA (4.31 g, 37.8 mmol). The mixture was stirred at room temperature for 3 h. The mixture was concentrated in vacuo to give 5-chloro-1'-[2-(4-{2,6-diazaspiro[3.3]heptane-2-carbonyl}-3-fluorophenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one. MS = 499.1 $[M+H]^+$.

Step 3: 5-chloro-1'-[2-(3-fluoro-4-{6-methanesulfonyl-2,6-diazaspiro[3.3]heptane-2-carbonyl}phenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 273)

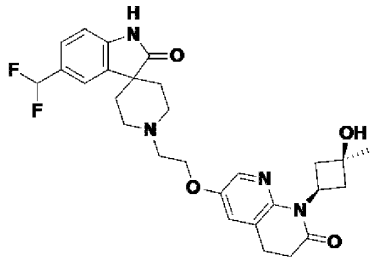


[1222] To a 0 °C solution of 5-chloro-1'-[2-(4-{2,6-diazaspiro[3.3]heptane-2-carbonyl}-3-fluorophenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (1.25 g, 2.51 mmol) in DCM (15 mL) was added TEA (1.74 mL, 12.5 mmol) and methanesulfonic anhydride (655 mg, 3.76 mmol). The mixture was stirred at room temperature for 3 h, and then was concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Kromasil C_{18} column, 25–55% MeCN:10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-[2-(3-fluoro-4-{6-methanesulfonyl-2,6-diazaspiro[3.3]heptane-2-carbonyl}phenoxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 273**). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.49 (s, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.44 (app t, J = 8.4 Hz, 1H), 7.23 (dd, J = 8.4, 2.0 Hz, 1H), 6.93 (dd, J = 12.4, 2.4 Hz, 1H), 6.89–6.83 (m,

2H), 4.20–4.18 (m, 6H), 4.03 (q, J = 8.8 Hz, 4H), 2.97 (s, 3H), 2.95–2.84 (m, 4H), 2.72–2.67 (m, 2H), 1.82–1.66 (m, 4H). MS = 577.2 $[M+H]^+$.

Example 58

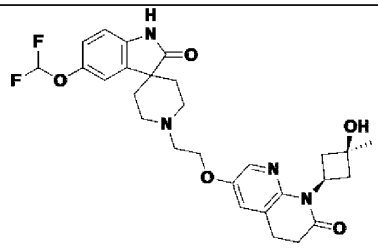
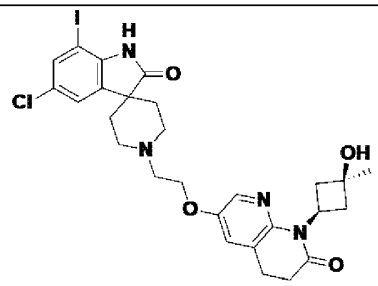
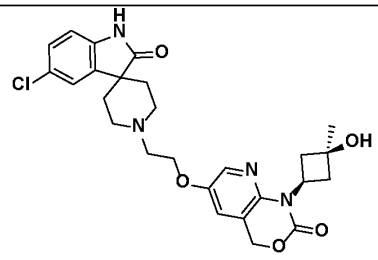
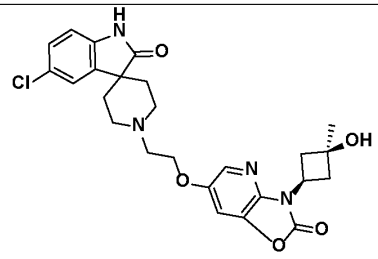
5-(difluoromethyl)-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 274)



[1223] To a solution of 6-(2-bromoethoxy)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (**Intermediate A-89**, 100 mg, 0.281 mmol) and 5-(difluoromethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-1**, 89.4 mg, 0.309 mmol, HCl salt) in MeCN (3 mL) was added $NaHCO_3$ (94.5 mg, 1.13 mmol). The mixture was stirred at 80 °C for 16 h. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters Xbridge BEH C_{18} column, 25–55% MeCN:10 mM NH_4HCO_3 in H_2O) to give 5-(difluoromethyl)-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 274**). ^1H NMR (400 MHz, DMSO-d_6): δ 10.62 (s, 1H), 7.94 (d, J = 2.4 Hz, 1H), 7.66 (s 1H), 7.43 – 7.39 (m, 2H), 7.10 – 6.82 (m, 2H), 4.82 (s, 1H), 4.24 (t, J = 8.0 Hz, 1H), 4.19 (t, J = 5.6 Hz, 2H), 2.96 – 2.94 (m, 2H), 2.86 (t, J = 5.6 Hz, 2H), 2.80 (t, J = 7.2 Hz, 2H), 2.72 – 2.67 (m, 2H), 2.44 – 2.42 (m, 4H), 2.34 (t, J = 7.2 Hz, 2H), 1.85 – 1.80 (m, 2H), 1.71 – 1.66 (m, 2H), 1.25 (s, 3H). MS = 527.3 $[M+H]^+$.

[1224] The following compound in **Table 38.1** was prepared according to the procedures similar to those described for **Compound 274** using the appropriate starting materials.

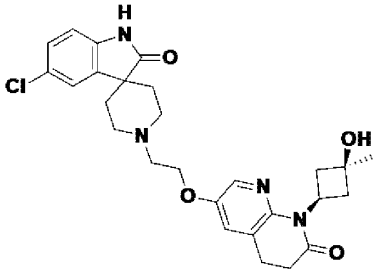
Table 38.1

No.	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Inter-mediate Used
325		5-(difluoromethoxy)-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 543.2 Found 543.1	**A-89** & **B-2**
329		5-chloro-7-iodo-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 637.1 Found 637.0	**A-89** & **B-24**
289		5-chloro-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H,2H,4H-pyrido[2,3-d][1,3]oxazin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 513.2 Found 513.2	**A-90** & **B-4**
394		5-chloro-1'-[2-({2-oxo-3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-2H,3H-[1,3]oxazolo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-	Calc'd 499.2 Found 499.2	**A-91** & **B-4**

		dihydrospiro[indole-3,4'-piperidin]-2-one		

Example 59

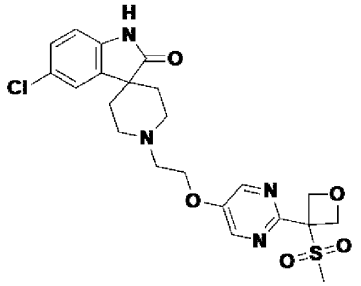
5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 275)



[1225] To a solution of 6-(2-bromoethoxy)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (**Intermediate A-89**, 330 mg, 0.929 mmol) and 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 279 mg, 1.02 mmol, HCl salt) in MeCN (10 mL) was added $NaHCO_3$ (234 mg, 2.79 mmol). The mixture was stirred at 80 °C for 12 h. After cooling to room temperature, the mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters Xbridge BEH C_{18} column, 20–50% MeCN:10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 275**). ^1H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 7.94 (d, J = 2.8 Hz, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.39 (d, J = 2.8 Hz, 1H), 7.23 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 4.82 (s, 1H), 4.30 – 4.22 (m, 1H), 4.18 (t, J = 5.6 Hz, 2H), 2.95 – 2.89 (m, 2H), 2.87 – 2.77 (m, 4H), 2.72 – 2.67 (m, 2H), 2.48 – 2.46 (m, 2H), 2.46 – 2.41 (m, 2H), 2.38 – 2.32 (m, 2H), 1.82 – 1.67 (m, 4H), 1.25 (s, 3H). MS = 511.1 $[M+H]^+$.

Example 60

5-chloro-1'-(2-{[2-(3-methanesulfonyloxetan-3-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 276)



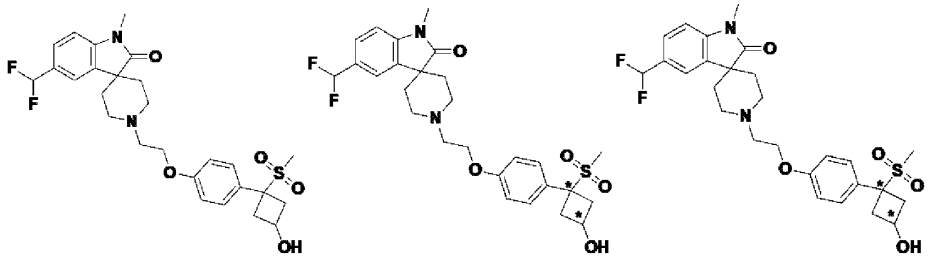
[1226] To a solution of 5-(2-bromoethoxy)-2-(3-methanesulfonyloxetan-3-yl)pyrimidine (**Intermediate A-88**, 50.0 mg, 0.148 mmol) and 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 38.6 mg, 0.163 mmol) in MeCN (4 mL) was added $NaHCO_3$ (62.3 mg, 0.744 mmol). The mixture was stirred at 80 °C for 15 h. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex C_{18} column, 15–45% MeCN:10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-(2-{[2-(3-methanesulfonyloxetan-3-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 276**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 1H), 8.71 (s, 2H), 7.50 (d, J = 2.0 Hz, 1H), 7.25 – 7.22 (m, 1H), 6.84 (d, J = 8.4 Hz, 1H), 5.20 (d, J = 7.6 Hz, 2H), 5.09 (d, J = 7.6 Hz, 2H), 4.38 (t, J = 5.6 Hz, 2H), 3.02 (s, 3H), 2.94 – 2.89 (m, 4H), 2.72 – 2.70 (m, 2H), 1.78 – 1.71 (m, 4H). MS = 493.1 $[M+H]^+$.

Example 61

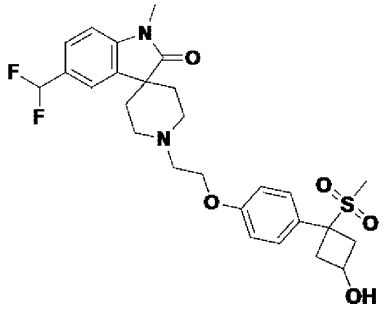
5-(difluoromethyl)-1'-{2-[4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenoxy]ethyl}-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 277),

5-(difluoromethyl)-1-methyl-1'-(2-{4-[(*cis*) or (*trans*)-3-hydroxy-1-methanesulfonylcyclobutyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 278), and

5-(difluoromethyl)-1-methyl-1'-(2-{4-[(*trans*) or (*cis*)-3-hydroxy-1-methanesulfonylcyclobutyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 279)

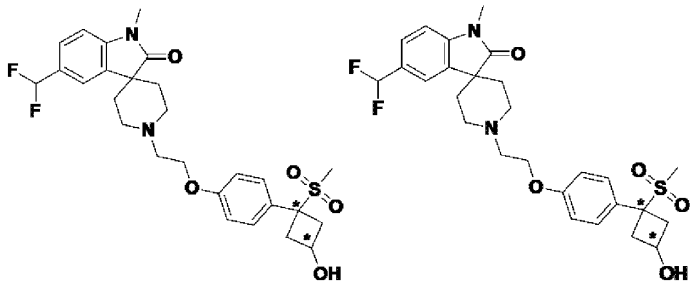


Step 1: 5-(difluoromethyl)-1'-{2-[4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenoxy]ethyl}-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 277)



[1227] To a solution of 2-[4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenoxy]ethyl methanesulfonate (**Example 54, Step 6,** 100 mg, 0.274 mmol) and 5-(difluoromethyl)-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-23**, 100 mg, 0.329 mmol, HCl salt) in MeCN (4 mL) was added $NaHCO_3$ (92.0 mg, 1.10 mmol). The mixture was stirred at 80 °C for 12 h. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex C_{18} column, 20–50% MeCN:10 mM NH_4HCO_3 in H_2O) to give 5-(difluoromethyl)-1'-{2-[4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenoxy]ethyl}-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 277**). MS = 535.2 $[M+H]^+$.

Step 2: 5-(difluoromethyl)-1-methyl-1'-(2-{4-[(*cis*) or (*trans*)-3-hydroxy-1-methanesulfonylcyclobutyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 278) and 5-(difluoromethyl)-1-methyl-1'-(2-{4-[(*trans*) or (*cis*)-3-hydroxy-1-methanesulfonylcyclobutyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 279)



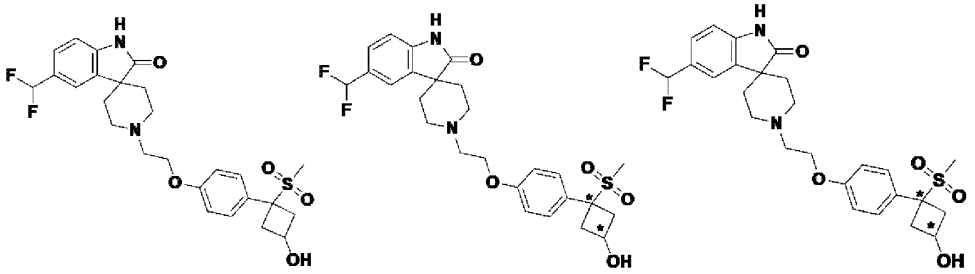
[1228] 5-(difluoromethyl)-1'-{2-[4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenoxy]ethyl}-1-methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one was purified by preparative chiral SFC (Daicel Chiralpak AD-3, 25–47% isopropanol with 0.1% NH_4OH in CO_2). The first eluting isomer of the title compound, **Compound 278**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.71 (s, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.48 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.0 Hz, 1H), 7.04 – 6.99 (m, 2H), 7.16 – 6.82 (m, 1H), 5.48 (d, J = 6.4 Hz, 1H), 4.18 (s, 2H), 3.89 – 3.79 (m, 1H), 3.15 (s, 3H), 2.97 (s, 2H), 2.91 – 2.80 (m, 4H), 2.77 – 2.67 (m, 4H), 2.54 (s, 3H), 1.88 – 1.67 (m, 4H). MS = 535.2 $[M+H]^+$. The second eluting isomer of the title compound, **Compound 279**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.71 (s, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.24 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.0 Hz, 1H), 7.01 – 6.98 (m, 2H), 7.16 – 6.84 (m, 1H), 5.33 (d, J = 6.8 Hz, 1H), 4.39 – 4.30 (m, 1H), 4.17 (t, J = 8.0 Hz, 2H), 3.29 – 3.23 (m, 2H), 3.15 (s, 3H), 3.00 – 2.93 (m, 2H), 2.90 – 2.84 (m, 2H), 2.75 – 2.68 (m, 2H), 2.64 (s, 3H), 2.44 – 2.37 (m, 2H), 1.86 – 1.68 (m, 4H). MS = 535.2 $[M+H]^+$.

Example 62

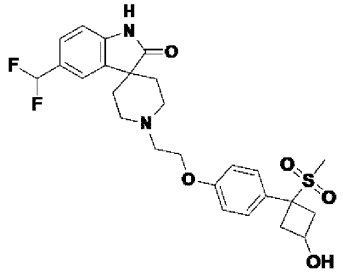
5-(difluoromethyl)-1'-{2-[4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 280),

5-(difluoromethyl)-1'-(2-{4-[(*cis*) or (*trans*)-3-hydroxy-1-methanesulfonylcyclobutyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 281), and

5-(difluoromethyl)-1'-(2-{4-[(*trans*) or (*cis*)-3-hydroxy-1-methanesulfonylcyclobutyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 282)

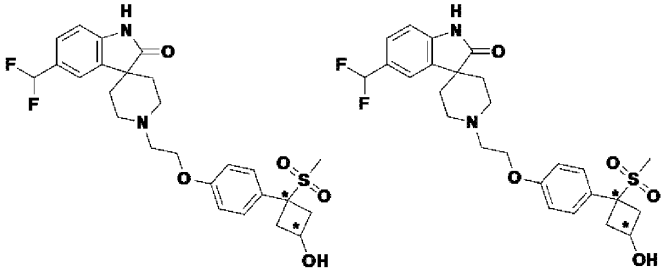


Step 1: 5-(difluoromethyl)-1'-{2-[4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 280)



[1229] To a solution of 2-[4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenoxy]ethyl methanesulfonate (**Example 54, Step 6,** 202 mg, 0.554 mmol) and 5-(difluoromethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-1**, 160 mg, 554 mmol, HCl salt) in MeCN (3 mL) was added $NaHCO_3$ (94.0 mg, 1.11 mmol). The mixture was stirred at 80 °C for 16 h. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters XBridge C_{18} column, 20–50% MeCN:10 mM NH_4HCO_3 in H_2O) to give 5-(difluoromethyl)-1'-{2-[4-(3-hydroxy-1-methanesulfonylcyclobutyl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 280**). MS = 521.2 $[M+H]^+$.

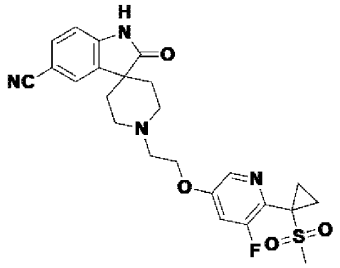
Step 2: 5-(difluoromethyl)-1'-(2-{4-[(*cis*) or (*trans*)-3-hydroxy-1-methanesulfonylcyclobutyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 281), and
5-(difluoromethyl)-1'-(2-{4-[(*trans*) or (*cis*)-3-hydroxy-1-methanesulfonylcyclobutyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 282)



[1230] 5-(Difluoromethyl)-1'-(2-{4-[(*cis*) or (*trans*)-3-hydroxy-1-methanesulfonylcyclobutyl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one was purified by preparative chiral SFC (Daicel Chiralpak AD-3, 40% isopropanol with 0.1% NH_4OH in CO_2). The first eluting isomer of the title compound, **Compound 281**: ^{1}H NMR (400 MHz, DMSO-d_6): 10.63 (s, 1H), 7.67 (s, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.0 Hz, 1H), 7.09 – 6.81 (m, 4H), 5.49 (d, J = 6.4 Hz, 1H), 4.18 (t, J = 4.8 Hz, 2H), 3.90 – 3.76 (m, 1H), 2.95 (s, 2H), 2.89 – 2.81 (m, 4H), 2.75 – 2.67 (m, 4H), 2.54 (s, 3H), 1.87 – 1.77 (m, 2H), 1.75 – 1.62 (m, 2H). MS = 521.2 $[M+H]^+$. The second eluting isomer of the title compound, **Compound 282**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.63 (s, 1H), 7.67 (s, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 8.8 Hz, 2H), 7.10 – 6.82 (m, 4H), 5.33 (d, J = 6.8 Hz, 1H), 4.38 – 4.28 (m, 1H), 4.16 (t, J = 5.6 Hz, 2H), 3.32 – 3.23 (m, 2H), 2.99 – 2.90 (m, 2H), 2.86 (t, J = 4.8 Hz, 2H), 2.70 (t, J = 7.6 Hz, 2H), 2.64 (s, 3H), 2.45 – 2.37 (m, 2H), 1.87 – 1.78 (m, 2H), 1.70 (s, 2H). MS = 521.2 $[M+H]^+$.

Example 63

1'-(2-{[5-fluoro-6-(1-methanesulfonylcyclopropyl)pyridin-3-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (Compound 283)



[1231] To a solution of 5-(2-bromoethoxy)-3-fluoro-2-(1-methanesulfonylcyclopropyl)pyridine (**Intermediate A-87**, 90.0 mg, 0.266 mmol) and 2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (**Intermediate B-9**, 78.0 mg, 0.293 mmol, HCl salt) in MeCN (1.5 mL) was added

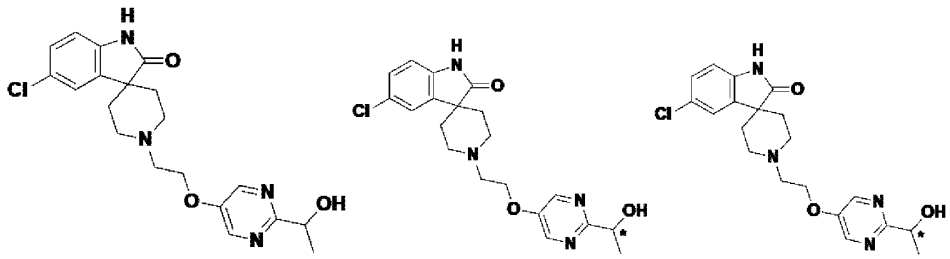
$NaHCO_3$ (112 mg, 1.33 mmol). The mixture was stirred at 80 °C for 15 h. After cooling to room temperature, solids were removed by filtration and the filtrate was purified by normal phase preparative TLC (SiO_2, EtOAc:MeOH = 10:1) to give 1'-(2-{[5-fluoro-6-(1-methanesulfonylcyclopropyl)pyridin-3-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile (**Compound 283**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.87 (s, 1H), 8.24 (d, J = 2.0 Hz, 1H), 7.96 (s, 1H), 7.68 – 7.54 (m, 2H), 7.00 (d, J = 8.0 Hz, 1H), 4.28 (s, 2H), 2.95 (s, 3H), 2.93 – 2.83 (m, 4H), 2.74 (d, J = 6.8 Hz, 2H), 1.84 – 1.69 (m, 6H), 1.39 – 1.36 (m, 2H). MS = 485.1 $[M+H]^+$.

Example 64

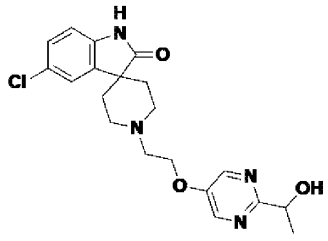
5-chloro-1'-(2-{[2-(1-hydroxyethyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 284),

5-chloro-1'-[2-({2-[(1*S*) or (1*R*)-1-hydroxyethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 285)

and 5-chloro-1'-[2-({2-[(1*R*) or (1*S*)-1-hydroxyethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 286)

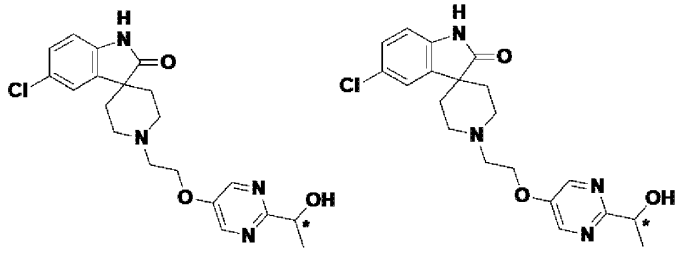


Step 1: 5-chloro-1'-(2-{[2-(1-hydroxyethyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one



[1232] A mixture of 1-[5-(2-bromoethoxy)pyrimidin-2-yl]ethan-1-ol (**Intermediate A-86**, 90.0 mg, 0.364 mmol), 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 91.0 mg, 0.382 mmol, HCl salt), and $NaHCO_3$ (153 mg, 1.82 mmol) in MeCN (5 mL) under N_2 atmosphere was stirred at 80 °C for 15 h. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 4 g cartridge, 0–20% MeOH:EtOAc) to give 5-chloro-1'-(2-{[2-(1-hydroxyethyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 284**) . ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 1H), 8.55 (s, 2H), 7.50 (d, J = 2.0 Hz, 1H), 7.23 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 5.10 (d, J = 5.6 Hz, 1H), 4.78 – 4.72 (m, 1H), 4.30 (t, J = 5.6 Hz, 2H), 2.92 – 2.65 (m, 4H), 2.71 – 2.69 (m, 2H), 1.78 – 1.70 (m, 4H), 1.38 (d, J = 6.8 Hz, 3H). MS = 403.2 $[M+H]^+$.

Step 2: 5-chloro-1'-[2-({2-[(1*S*) or (1*R*)-1-hydroxyethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 285) and 5-chloro-1'-[2-({2-[(1*R*) or (1*S*)-1-hydroxyethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 286)

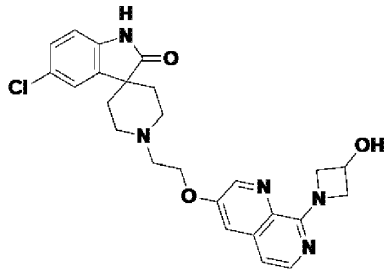


[1233] 5-chloro-1'-(2-{[2-(1-hydroxyethyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (100 mg, 0.248 mmol) was purified by preparative chiral SFC (Daicel Chiralpak IC-3, 55% MeOH with 0.1% NH_4OH in CO_2). The first eluting enantiomer of the title compound, **Compound 285**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 8.55 (s, 2H), 7.50 (d, J = 2.4 Hz, 1H), 7.23 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 5.10 (d, J = 5.6 Hz, 1H), 4.80 – 4.71 (m, 1H), 4.30 (t, J = 5.6 Hz, 2H), 2.95 – 2.85 (m, 4H), 2.72 – 2.66 (m, 2H), 1.82 – 1.75 (m, 2H), 1.73 – 1.66 (m, 2H), 1.39 (d, J = 6.4 Hz, 3H). MS = 403.2 $[M+H]^+$. The second eluting enantiomer of the title compound, **Compound 286**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 8.55 (d, J = 2.4 Hz, 2H), 7.50 (s, 1H), 7.23 (d, J = 8.4 Hz, 1H), 6.84 (dd, J = 8.4 Hz, 2.0 Hz,

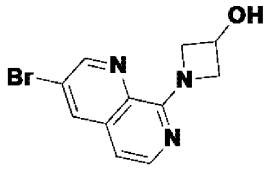
1H), 5.10 (dd, J = 5.6 Hz, 2.0 Hz, 1H), 4.80 – 4.71 (m, 1H), 4.30 (t, J = 4.0 Hz, 2H), 2.94 – 2.84 (m, 4H), 2.73 – 2.67 (m, 2H), 1.81 – 1.66 (m, 4H), 1.39 (d, J = 6.8 Hz, 3H). MS = 403.2 $[M+H]^+$.

Example 65

5-chloro-1'-(2-{[8-(3-hydroxyazetidin-1-yl)-1,7-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 314)

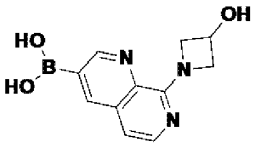


Step 1: 1-(3-bromo-1,7-naphthyridin-8-yl)azetidin-3-ol



[1234] A mixture of 3-bromo-8-chloro-1,7-naphthyridine (500 mg, 2.05 mmol), azetidin-3-ol (270 mg, 2.46 mmol), and diisopropylethylamine (663 mg, 5.13 mmol) in DMF (5 mL) was stirred at 50 °C for 16 h. After cooling to room temperature, the mixture was diluted with EtOAc (10 mL), and H_2O (20 mL) was then added. A precipitated solid was collected by filtration, and dried in vacuo to give 1-(3-bromo-1,7-naphthyridin-8-yl)azetidin-3-ol, which was used in the next step without further purification. MS = 280.0 / 282.0 $[M+H]^+$.

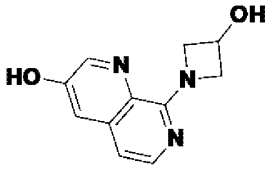
Step 2: [8-(3-hydroxyazetidin-1-yl)-1,7-naphthyridin-3-yl]boronic acid



[1235] A mixture of 1-(3-bromo-1,7-naphthyridin-8-yl)azetidin-3-ol (250 mg, 0.892 mmol), bis(pinacolato)diboron (272 mg, 1.07 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (36.0 mg,

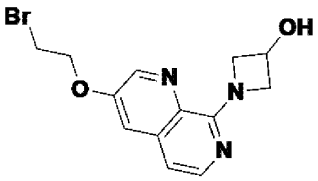
0.045 mmol) and KOAc (219 mg, 2.21 mmol) in 1,4-dioxane (15 mL) was purged with N_2 for 10 min, then stirred at 90 °C under N_2 for 16 h. The mixture was cooled to room temperature, filtered over a celite pad, and then washed with EtOAc (30 mL). The filtrate was concentrated in vacuo to give [8-(3-hydroxyazetidin-1-yl)-1,7-naphthyridin-3-yl]boronic acid, which was used in the next step without further purification. MS = 246.2 $[M+H]^+$.

Step 3: 8-(3-hydroxyazetidin-1-yl)-1,7-naphthyridin-3-ol



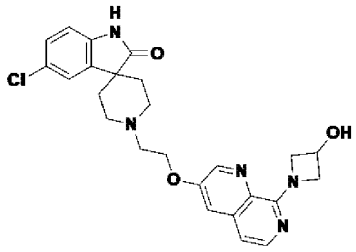
[1236] [8-(3-Hydroxyazetidin-1-yl)-1,7-naphthyridin-3-yl]boronic acid (0.892 mmol) was dissolved in MeOH (5 mL) and cooled to 0 °C. 30% H_2O_2 in H_2O (0.228 mL, 2.23 mmol) was then added dropwise. The resulting mixture was stirred at room temperature for 3 h, then concentrated in vacuo to give 8-(3-hydroxyazetidin-1-yl)-1,7-naphthyridin-3-ol, which was used in the next step without further purification. MS = 218.1 $[M+H]^+$.

Step 4: 1-(3-(2-bromoethoxy)-1,7-naphthyridin-8-yl)azetidin-3-ol



[1237] A mixture of 8-(3-hydroxyazetidin-1-yl)-1,7-naphthyridin-3-ol (220 mg, 1.01 mmol) and Cs_2CO_3 (660 mg, 2.03 mmol) in 1,2-dibromoethane (3.50 mL, 40.5 mmol) and DMF (1 mL) was stirred at 90 °C for 3 h. The mixture was cooled to room temperature and filtered over a celite pad. The filtrate was concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 25 g cartridge, 0–10% MeOH/DCM) to give 1-[3-(2-bromoethoxy)-1,7-naphthyridin-8-yl]azetidin-3-ol. MS = 324.1 / 326.1 $[M+H]^+$.

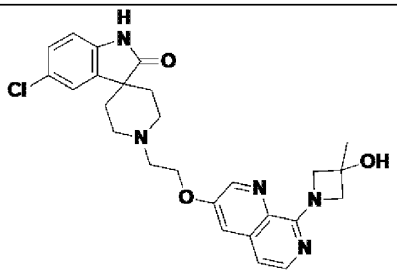
Step 5: 5-chloro-1'-(2-{[8-(3-hydroxyazetidin-1-yl)-1,7-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 314)

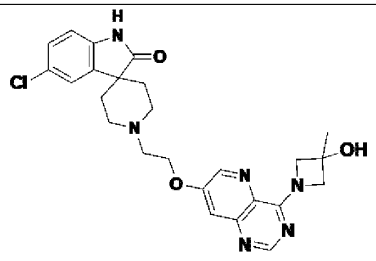
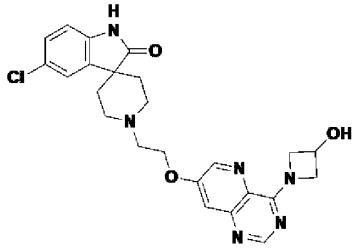


[1238] A mixture of 1-[3-(2-bromoethoxy)-1,7-naphthyridin-8-yl]azetidin-3-ol (45.0 mg, 0.139 mmol), 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 39.8 mg, 0.146 mmol, HCl salt), K_2CO_3 (48.0 mg, 0.347 mmol) and KI (12.0 mg, 0.069 mmol) in DMF (1.0 mL) was stirred at 60 °C for 16 h. The mixture was then cooled to room temperature and filtered over a celite pad. The filtrate was concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex Kinetex C_{18} column, 5–50% MeCN in H_2O with 0.1% NH_4OH modifier) to give 5-chloro-1'-(2-{[8-(3-hydroxyazetidin-1-yl)-1,7-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 314**). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.42 (s, 1H), 8.40 (d, J = 2.9 Hz, 1H), 7.82 (d, J = 5.6 Hz, 1H), 7.54 (d, J = 2.9 Hz, 1H), 7.44 (d, J = 2.2 Hz, 1H), 7.17 (dd, J = 8.2 Hz, 2.1 Hz, 1H), 6.82 (d, J = 5.6 Hz, 1H), 6.78 (d, J = 8.3 Hz, 1H), 5.53 (d, J = 5.6 Hz, 1H), 4.54 – 4.49 (m, 3H), 4.24 (t, J = 5.7 Hz, 2H), 4.03 – 3.99 (m, 2H), 2.92 – 2.83 (m, 4H), 2.70 – 2.61 (m, 2H), 1.78 – 1.60 (m, 4H). MS = 480.2 $[M+H]^+$.

[1239] The following compound in **Table 38.2** was prepared according to the procedures similar to those described for **Compound 314** using the appropriate starting materials.

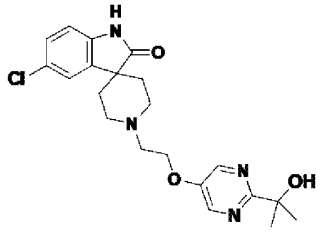
Table 38.2

No.	Structure	IUPAC Name	Exact Mass $[M+H]^+$
306		5-chloro-1'-(2-{[8-(3-hydroxy-3-methylazetidin-1-yl)-1,7-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 494.2 Found 494.2

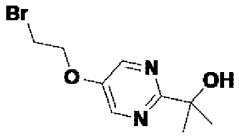
364		5-chloro-1'-(2-{[4-(3-hydroxy-3-methylazetidin-1-yl)pyrido[3,2-d]pyrimidin-7-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 495.2 Found 495.2
366		5-chloro-1'-(2-{[4-(3-hydroxyazetidin-1-yl)pyrido[3,2-d]pyrimidin-7-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 481.2 Found 481.2

Example 66

5-chloro-1'-(2-{[2-(2-hydroxypropan-2-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 305)



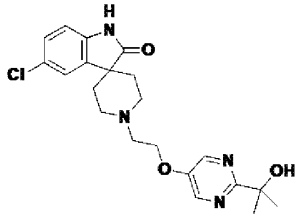
Step 1: 2-(5-(2-bromoethoxy)pyrimidin-2-yl)propan-2-ol



[1240] A mixture of 2-(2-hydroxypropan-2-yl)pyrimidin-5-ol (120 mg, 0.778 mmol) and Cs_2CO_3 (507 mg, 1.56 mmol) in 1,2-dibromoethane (2.7 mL, 31.5 mmol) and DMF (0.3 mL) was stirred at 90 °C for 3 h. The mixture was cooled to room

temperature and filtered over a celite pad, and the filtrate was concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 25 g cartridge, 0–70% EtOAc/Hexane) to give 2-[5-(2-bromoethoxy)pyrimidin-2-yl]propan-2-ol. MS = 261.1 / 263.1 $[M+H]^+$.

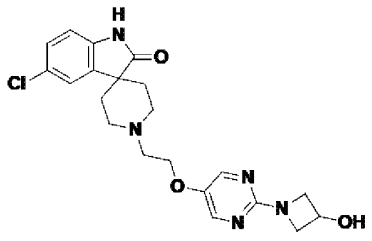
Step 2: 5-chloro-1'-(2-{[2-(2-hydroxypropan-2-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 305)



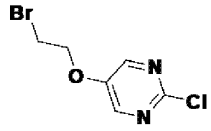
[1241] A mixture of 2-[5-(2-bromoethoxy)pyrimidin-2-yl]propan-2-ol (51.0 mg, 0.195 mmol), 5-chloro-1H-spiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 58.7 mg, 0.215 mmol, HCl salt), K_2CO_3 (67.0 mg, 0.488 mmol), and KI (16 mg, 0.098 mmol) in DMF (2.0 mL) was stirred at 60 °C for 16 h. The mixture was cooled to room temperature and filtered over a celite pad. The filtrate was concentrated in vacuo, and the residue was purified by reverse phase preparative HPLC (5–40% MeCN in H_2O with 0.1% formic acid modifier) to give 5-chloro-1'-(2-{[2-(2-hydroxypropan-2-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 305**). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.47 (s, 1H), 8.50 (s, 2H), 7.45 – 7.41 (m, 1H), 7.19 (dd, J = 8.3 Hz, 2.1 Hz, 1H), 6.79 (d, J = 8.3 Hz, 1H), 4.88 (s, 1H), 4.32 – 4.28 (m, 2H), 3.11 – 2.47 (m, 6H), 2.00 – 1.48 (m, 4H), 1.41 (s, 6H). MS = 417.2 $[M+H]^+$.

Example 67

5-chloro-1'-(2-{[2-(3-hydroxyazetidin-1-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 301)

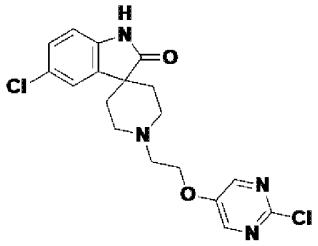


Step 1: 5-(2-bromoethoxy)-2-chloropyrimidine



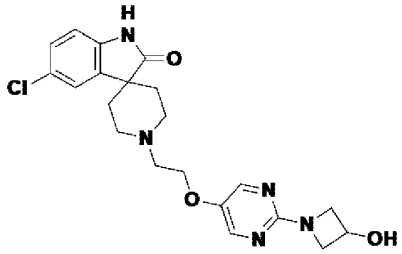
[1242] To a solution of 2-chloropyrimidin-5-ol (1.00 g, 7.66 mmol) in DMF (7.7 mL) was added 1,2-dibromoethane (15.3 mL, 194 mmol) and Cs_2CO_3 (7.49 g, 23.0 mmol). The mixture was stirred at 90 °C for 16 h. The mixture was cooled to room temperature and filtered over a celite pad, and the filtrate was concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 50 g cartridge, 0–100% EtOAc/Hexanes) to give 5-(2-bromoethoxy)-2-chloropyrimidine as a yellow oil. MS = 237.0 $[M+H]^+$.

Step 2: 5-chloro-1'-{2-[(2-chloropyrimidin-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one



[1243] To a vial was added 5-(2-bromoethoxy)-2-chloropyrimidine (1.23 g, 3.13 mmol), 5-chloro-1H-spiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 1.34 g, 4.92 mmol, HCl salt), K_2CO_3 (2.15 g, 15.5 mmol), KI (860 mg, 5.18 mmol), and DMF (17.3 mL). The mixture was stirred at 65 °C for 4 h. After cooling to room temperature, the mixture was diluted with H_2O (100 mL). The resulting solids were isolated by filtration and dried in vacuo to give 5-chloro-1'-{2-[(2-chloropyrimidin-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one, which was used in the subsequent step without further purification. MS = 393.2 $[M+H]^+$.

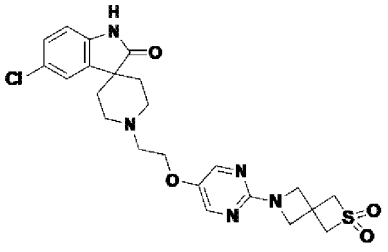
Step 3: 5-chloro-1'-(2-{[2-(3-hydroxyazetidin-1-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 301)

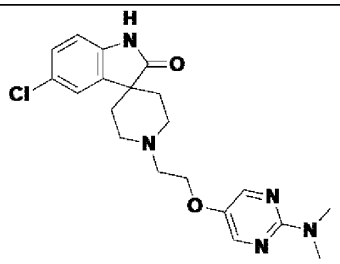
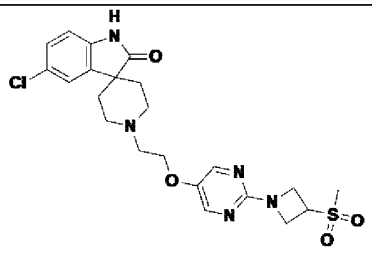
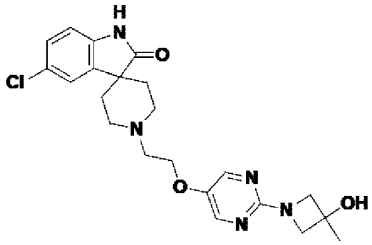
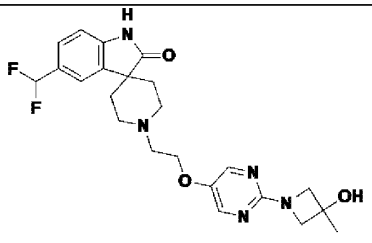


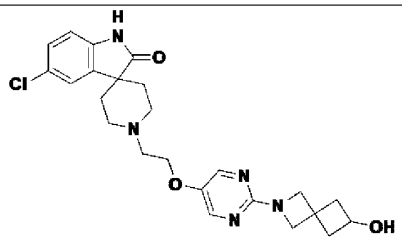
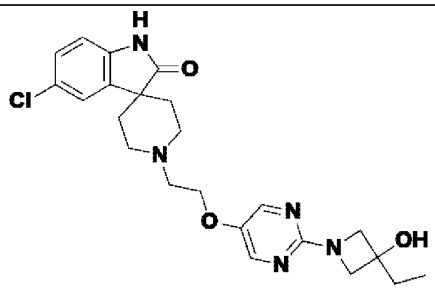
[1244] To a microwave vial was added azetidin-3-ol (63.0 mg, 0.575 mmol, HCl salt), 5-chloro-1'-{2-[(2-chloropyrimidin-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (75.0 mg, 0.191 mmol), DMSO (0.38 mL), and TEA (0.058 g, 0.572 mmol). The reaction stirred at 100 °C for 1 h under microwave irradiation (normal absorption). The reaction was cooled to room temperature and diluted with H_2O (1 mL) and MeCN (1 mL). The mixture was purified by reverse phase C_{18} chromatography (Biotage SFär C_{18} Duo cartridge, 5–50% MeCN in H_2O with 0.1% NH_4OH modifier) to give 5-chloro-1'-(2-{[2-(3-hydroxyazetidin-1-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 301**). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.48 (s, 1H), 8.21 (s, 2H), 7.50 (d, J = 2.2 Hz, 1H), 7.23 (dd, J = 8.3 Hz, 2.1 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 5.61 (d, J = 5.7 Hz, 1H), 4.56 – 4.49 (m, 1H), 4.18 – 4.08 (m, 4H), 3.74 – 3.68 (m, 2H), 2.93 – 2.86 (m, 2H), 2.80 (t, J = 5.7 Hz, 2H), 2.70 – 2.62 (m, 2H), 1.80 – 1.66 (m, 4H). MS = 430.2 $[M+H]^+$.

[1245] The following compounds in **Table 38.4** were prepared according to the procedures similar to those described for **Compound 301** using the appropriate starting materials.

Table 38.4

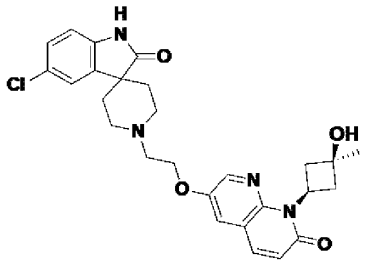
No.	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Inter-mediate Used
304		6-[5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)pyrimidin-2-yl]-2λ^6-thia-6-	Calc'd 504.1 Found 504.2	**B-4**

		azaspiro[3.3]heptane-2,2-dione		
303		5-chloro-1'-(2-{[2-(dimethylamino)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 402.2 Found 402.2	**B-4**
302		5-chloro-1'-(2-{[2-(3-methanesulfonylazetidin-1-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 492.1 Found 492.1	**B-4**
300		5-chloro-1'-(2-{[2-(3-hydroxy-3-methylazetidin-1-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 444.2 Found 444.2	**B-4**
395		5-(difluoromethyl)-1'-(2-{[2-(3-hydroxy-3-methylazetidin-1-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-	Calc'd 460.2 Found 460.2	**B-1**

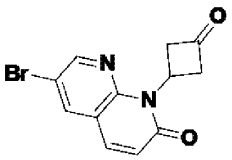
		dihydrospiro[indole-3,4'-piperidin]-2-one		
396		5-chloro-1'-{2-[(2-{6-hydroxy-2-azaspiro[3.3]heptan-2-yl}pyrimidin-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 470.0 Found 470.2	**B-4**
397		5-chloro-1'-(2-{[2-(3-ethyl-3-hydroxyazetidin-1-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 458.2 Found 458.2	**B-4**

Example 68

5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 323)

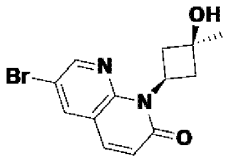


Step 1: 6-bromo-1-(3-oxocyclobutyl)-1,2-dihydro-1,8-naphthyridin-2-one



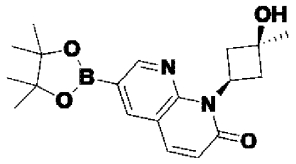
[1246] A mixture of 6-bromo-1-(3-oxocyclobutyl)-1,2-dihydro-1,8-naphthyridin-2-one (5.00 g, 22.2 mmol) and K_2CO_3 (4.61 g, 33.3 mmol) in DMF (50 mL) was stirred at 50 °C for 1 h under N_2 atmosphere. 3-Bromocyclobutanone (4.63 g, 31.1 mmol) was added to the mixture, which was stirred for an additional 13 h. After cooling to 0 °C, the reaction mixture was quenched with H_2O (100 mL) and extracted with EtOAc (3 x 60 mL). The combined organic layers were washed with brine (3 x 60 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give 6-bromo-1-(3-oxocyclobutyl)-1,2-dihydro-1,8-naphthyridin-2-one, which was taken on to the subsequent step without further purification. MS = 293.0 / 295.0 $[M+H]^+$.

Step 2: 6-bromo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1,2-dihydro-1,8-naphthyridin-2-one



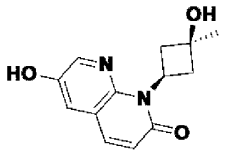
[1247] To a three-neck round-bottom flask equipped with a magnetic stir bar and thermometer was added 6-bromo-1-(3-oxocyclobutyl)-1,8-naphthyridin-2-one (6.30 g, 21.5 mmol) and THF (65 mL). The mixture was cooled to 0 °C and 3.0 M MeMgBr in 2-MeTHF (7.88 mL, 23.6 mmol) was added dropwise. After stirring at 0 °C for 2 h, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 40 g cartridge, 0–100% EtOAc/Petroleum ether). The resulting crude product was triturated with 1:5 EtOAc/Petroleum ether to give 6-bromo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1,2-dihydro-1,8-naphthyridin-2-one. MS = 309.1 / 311.1 $[M+H]^+$.

Step 3: 1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-1,8-naphthyridin-2-one



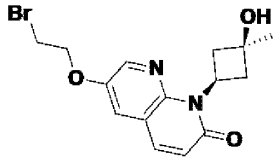
[1248] To a solution of 6-bromo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1,2-dihydro-1,8-naphthyridin-2-one (3.48 g, 11.3 mmol) in 1,4-dioxane (40 mL) was added bis(pinacolato)diboron (4.29 g, 16.9 mmol), KOAc (2.76 g, 28.1 mmol) and Pd(dppf)Cl_2 (412 mg, 0.563 mmol). The mixture was degassed and purged with N_2 (3x), and then the mixture was stirred at 80 °C for 16 h under N_2 atmosphere. After cooling to room temperature, the mixture was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 40 g cartridge, 0–100% EtOAc/Petroleum ether) to give 1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-1,8-naphthyridin-2-one.

Step 4: 6-hydroxy-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1,2-dihydro-1,8-naphthyridin-2-one



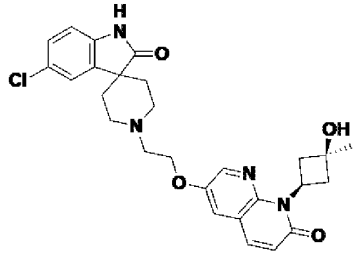
[1249] To a solution of 1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-1,8-naphthyridin-2-one (3.10 g, 8.70 mmol) in THF (15 mL) and H_2O (15 mL) was added Oxone (3.74 g, 6.09 mmol). The mixture was stirred at 0 °C for 2 h. The 0 °C reaction mixture was quenched by addition of saturated aqueous Na_2SO_3 (30 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give 6-hydroxy-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1,2-dihydro-1,8-naphthyridin-2-one, which was used in the subsequent step without further purification. MS = 247.2 $[M+H]^+$.

Step 5: 6-(2-bromoethoxy)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1,2-dihydro-1,8-naphthyridin-2-one



[1250] To a solution of 6-hydroxy-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1,2-dihydro-1,8-naphthyridin-2-one (2.40 g, 9.75 mmol) in MeCN (25 mL) was added K_2CO_3 (5.39 g, 39.0 mmol) and 1,2-dibromoethane (29.4 mL, 390 mmol). The mixture was stirred at 65 °C for 16 h. After cooling to room temperature, the mixture was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 40 g cartridge, 0–100% EtOAc/Petroleum ether) to give 6-(2-bromoethoxy)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1,2-dihydro-1,8-naphthyridin-2-one. MS = 353.1 / 355.1 $[M+H]^+$.

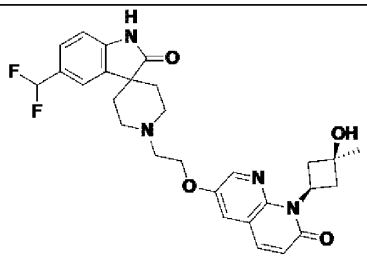
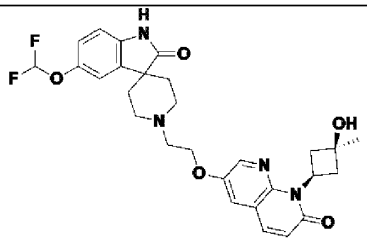
Step 6: 5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 323)



[1251] To a solution of 6-(2-bromoethoxy)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1,2-dihydro-1,8-naphthyridin-2-one (1.00 g, 2.83 mmol) in MeCN (12 mL) was added $NaHCO_3$ (951 mg, 11.3 mmol) and 5-chloro-1H-spiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 851 mg, 3.11 mmol, HCl salt). The mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the mixture was filtered, and the filter cake was triturated with H_2O (10 mL). The filter cake was dried in vacuo to give 5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 323**). ^1H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 8.40 (d, J = 3.2 Hz, 1H), 7.88 – 7.82 (m, 2H), 7.49 (d, J = 2.0 Hz, 1H), 7.23 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.64 (d, J = 9.6 Hz, 1H), 5.35 – 5.24 (m, 1H), 4.94 (s, 1H), 4.26 (t, J = 5.6 Hz, 2H), 3.00 – 2.88 (m, 6H), 2.74 – 2.65 (m, 2H), 2.43 – 2.36 (m, 2H), 1.82 – 1.67 (m, 4H), 1.33 (s, 3H). MS = 509.1 $[M+H]^+$.

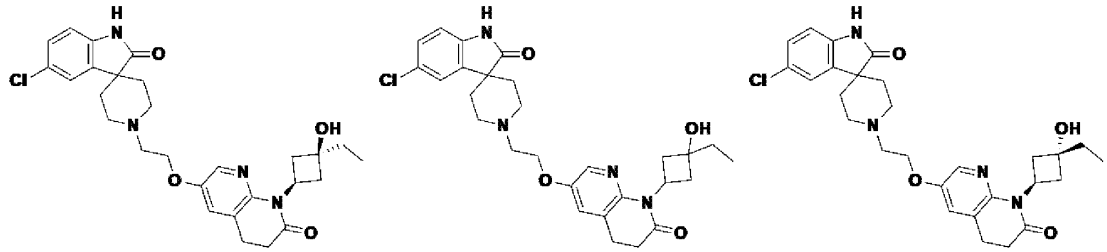
[1252] The following compounds in **Table 38.5** were prepared according to the procedures similar to those described for **Compound 323** using the appropriate starting materials.

Table 38.5

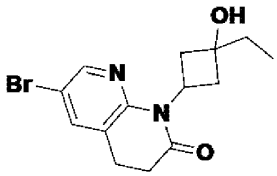
No.	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Intermediate used
324		5-(difluoromethyl)-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 525.2 Found 525.2	B-1
325		5-(difluoromethoxy)-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 541.2 Found 541.3	B-2

Example 69

5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-ethyl-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 321), 5-chloro-1'-[2-({7-oxo-8-[(3-ethyl-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 318), and 5-chloro-1'-[2-({7-oxo-8-[(*trans*)-3-ethyl-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 290)

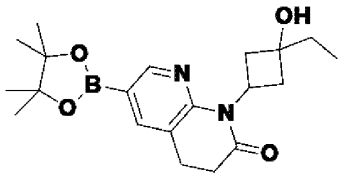


Step 1: 6-bromo-1-(3-ethyl-3-hydroxycyclobutyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



[1253] To a 0 °C solution of 6-bromo-1-(3-oxocyclobutyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (**Procedure for Intermediate A-79, Step 1**, 5.00 g, 16.9 mmol) in THF (100 mL) under N_2 atmosphere was added 3.0 M EtMgBr in 2-MeTHF (8.47 mL, 25.4 mmol). The mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (80 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–80% EtOAc/Petroleum ether) to give 6-bromo-1-(3-ethyl-3-hydroxycyclobutyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one. MS = 325.1 / 327.1 $[M+H]^+$.

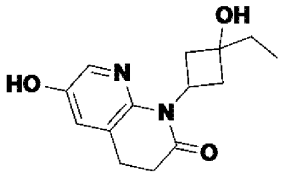
Step 2: 1-(3-ethyl-3-hydroxycyclobutyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



[1254] To a solution of 6-bromo-1-(3-ethyl-3-hydroxycyclobutyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (1.40 g, 4.31 mmol) and bis(pinacolato)diboron (1.20 g, 4.74 mmol) in 1,4-dioxane (30 mL) was added KOAc (1.27 g, 12.9 mmol) and $Pd(dppf)Cl_2$ (352 mg, 0.431 mmol).

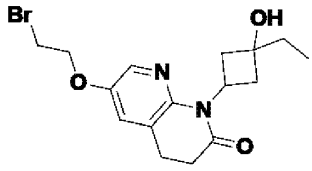
The mixture was purged with N_2 (3x), and then the mixture was stirred at 80 °C for 16 h under N_2 atmosphere. After cooling to room temperature, the reaction mixture was filtered, and the filtrate was concentrated in vacuo to give 1-(3-ethyl-3-hydroxycyclobutyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one, which was used in the subsequent step without further purification. MS = 373.2 $[M+H]^+$.

Step 3: 1-(3-ethyl-3-hydroxycyclobutyl)-6-hydroxy-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



[1255] To a 0 °C solution of 1-(3-ethyl-3-hydroxycyclobutyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (1.60 g, 4.30 mmol) in acetone (40 mL) and H_2O (5 mL) was added Oxone (2.91 g, 4.73 mmol), and then the mixture was stirred at room temperature for 1 h. The reaction mixture was filtered, and the filtrate was diluted with H_2O (40 mL) and extracted with EtOAc (4 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Isco 12 g cartridge, 0–100% EtOAc/Petroleum ether) to give 1-(3-ethyl-3-hydroxycyclobutyl)-6-hydroxy-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one. MS = 263.2 $[M+H]^+$.

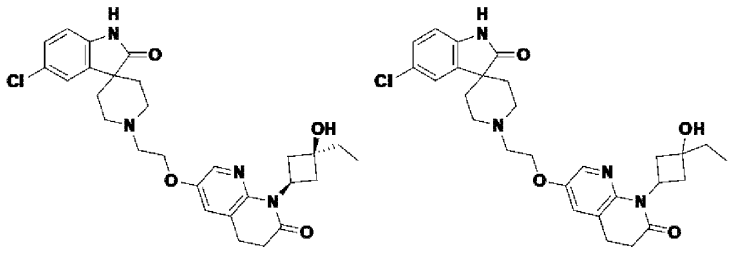
Step 4: 6-(2-bromoethoxy)-1-(3-ethyl-3-hydroxycyclobutyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



[1256] To a solution of 1-(3-ethyl-3-hydroxycyclobutyl)-6-hydroxy-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (400 mg, 1.52 mmol) in MeCN (0.5 mL) and 1,2-dibromoethane (4.60 mL, 61.0 mmol) was added K_2CO_3 (422 mg, 3.05 mmol). The mixture was then stirred at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 8

g cartridge, 0–100% EtOAc/Petroleum ether) to give 6-(2-bromoethoxy)-1-(3-ethyl-3-hydroxycyclobutyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one. MS = 369.1 / 371.1 $[M+H]^+$.

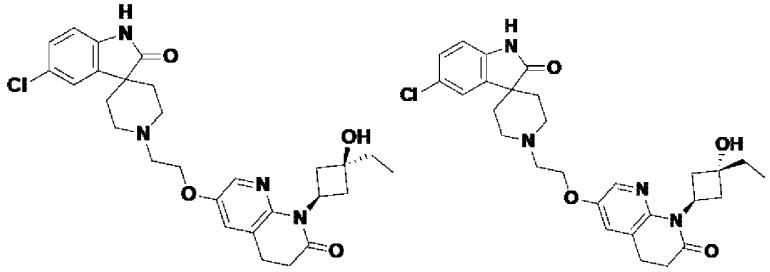
Step 5: 5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-ethyl-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 321) and 5-chloro-1'-[2-({7-oxo-8-[(3-ethyl-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 318)



[1257] To a solution of 6-(2-bromoethoxy)-1-(3-ethyl-3-hydroxycyclobutyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (250 mg, 0.677 mmol) and 5-chloro-1H-spiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 203 mg, 0.745 mmol, HCl salt) in MeCN (5 mL) was added $NaHCO_3$ (228 mg, 2.71 mmol). The mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters Xbridge OBD C_{18} column, 25–55% MeCN:10 mM NH_4HCO_3 in H_2O). Baseline separation of the major (cis) and minor (trans) products was not obtained. The first eluting fractions of product provided 5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-ethyl-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 321**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 7.94 (t, J = 2.8 Hz, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.40 (d, J = 2.8 Hz, 1H), 7.25 – 7.22 (m, 1H), 6.84 (d, J = 8.0 Hz, 1H), 4.66 (s, 1H), 4.22 – 4.16 (m, 3H), 2.92 – 2.78 (m, 6H), 2.69 – 2.65 (m, 2H), 2.50 – 2.49 (m, 4H), 2.27 – 2.26 (m, 2H), 1.78 – 1.72 (m, 4H), 1.51 – 1.49 (m, 2H), 0.87 (t, J = 7.2 Hz, 3H). MS = 525.2 $[M+H]^+$. Remaining fractions were a mixture of cis and trans products, providing 5-chloro-1'-[2-({7-oxo-8-[(3-ethyl-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 318**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 7.95 – 7.94 (m, 1H), 7.51 (s, 1H), 7.50 – 7.38 (m, 1H), 7.25 – 7.22 (m,

1H), 6.84 (d, J = 8.4 Hz, 1H), 5.39 – 5.28 (m, 0.3H), 4.67 – 4.61 (m, 1H), 4.24 – 4.16 (m, 2.6H), 2.92 – 2.78 (m, 6H), 2.69 – 2.54 (m, 6H), 2.27 – 2.12 (m, 2H), 1.78 – 1.72 (m, 4H), 1.51 – 1.49 (m, 2H), 0.88 – 0.81 (m, 3H). MS = 525.2 $[M+H]^+$.

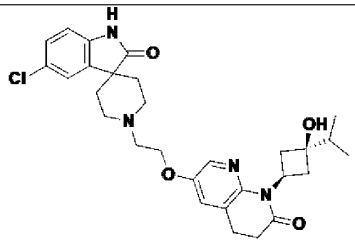
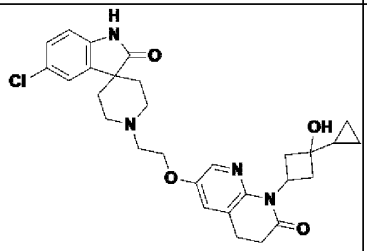
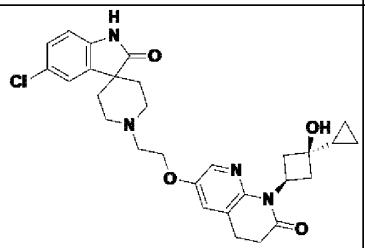
Step 6: 5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-ethyl-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 321) and 5-chloro-1'-[2-({7-oxo-8-[(*trans*)-3-ethyl-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 290)

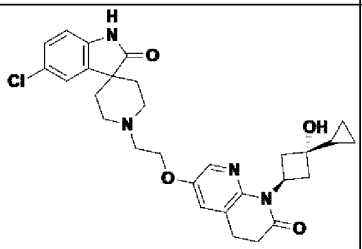


[1258] 5-chloro-1'-[2-({7-oxo-8-[(3-ethyl-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 318**, 220 mg, 0.419 mmol) was separated by preparative chiral SFC (Daicel Chiralpak AD-3 column, 60% IPA with 0.1% NH_4OH in CO_2). The first eluting diastereomer of the title compound, 5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-ethyl-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 321**). The second eluting diastereomer of the title compound, 5-chloro-1'-[2-({7-oxo-8-[(*trans*)-3-ethyl-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one **(Compound 290)**: ^1H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 7.95 (d, J = 2.8 Hz, 1H), 7.50 (s, 1H), 7.38 (d, J = 2.4 Hz, 1H), 7.25 – 7.22 (m, 1H), 6.84 (d, J = 8.0 Hz, 1H), 5.37 – 5.28 (m, 1H), 4.61 (s, 1H), 4.18 (t, J = 5.2 Hz, 2H), 2.92 – 2.78 (m, 6H), 2.69 – 2.62 (m, 6H), 2.13 – 2.12 (m, 2H), 1.76 – 1.72 (m, 4H), 1.56 – 1.55 (m, 2H), 0.81 (t, J = 7.2 Hz, 3H). MS = 525.2 $[M+H]^+$.

[1259] The following compounds in **Table 38.6** were prepared according to the procedures similar to those described for **Compounds 290, 318, & 321** using the appropriate starting materials.

Table 38.6

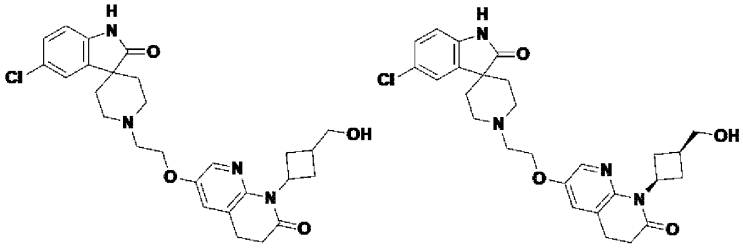
No.	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Comments	Elution Order	Chiral Column
317		5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-(propan-2-yl)cyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 539.2 Found 539.3	Route only provided cis isomer	n/a	n/a
299		5-chloro-1'-(2-{[8-(3-cyclopropyl-3-hydroxycyclobutyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 537.2 Found 537.4	Step 5 provided a mixture of isomers	n/a	n/a
398		5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-cyclopropyl-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-	Calc'd 537.2 Found 537.3	n/a	2nd	Daicel Chiralpak IF

		dihydrospiro[indole-3,4'-piperidin]-2-one				
297		5-chloro-1'-[2-({7-oxo-8-[(*trans*)-3-cyclopropyl-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 537.2 Found 537.1	n/a	1st	Daicel Chiralpak IF

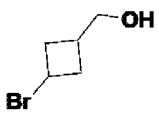
Example 70

5-chloro-1'-[2-({8-[3-(hydroxymethyl)cyclobutyl]-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one and (Compound 326)

5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-(hydroxymethyl)cyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 319)



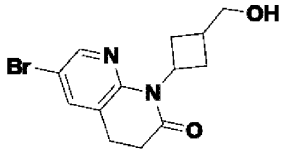
Step 1: (3-bromocyclobutyl)methanol



[1260] To a 0 °C solution of methyl 3-bromocyclobutane-1-carboxylate (5.00 g, 25.9 mmol) in THF (50 mL) under N_2 atmosphere was added 4.0 M $LiBH_4$ in THF (9.71 mL, 38.8 mmol). The mixture was stirred at room temperature for 2 h. The mixture was diluted with saturated aqueous

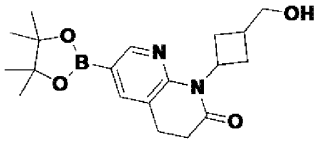
NH_4Cl (150 mL) and extracted with EtOAc (3 x 100 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 20 g cartridge, 0–100% EtOAc/Petroleum ether) to give (3-bromocyclobutyl)methanol. ^1H NMR (400 MHz, $CDCl_3$, 8/9 H): δ 4.60 – 4.52 (m, 1H) 3.66 (d, J = 6.4 Hz, 2H) 2.79 – 2.76 (m, 1H) 2.61 – 2.53 (m, 4H)

Step 2: 6-bromo-1-[3-(hydroxymethyl)cyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



[1261] To a solution of 6-bromo-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (2.00 g, 8.81 mmol) in DMF (25 mL) was added Cs_2CO_3 (5.74 g, 17.6 mmol), NaI (2.64 g, 17.6 mmol) and (3-bromocyclobutyl)methanol (2.91 g, 17.6 mmol). The mixture was stirred at 130 °C for 16 h. After cooling to room temperature, the residue was diluted with H_2O (50 mL), extracted with EtOAc (3 x 30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 20 g cartridge, 0–100% EtOAc/Petroleum ether) to give 6-bromo-1-[3-(hydroxymethyl)cyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one. MS = 311.0 / 313.0 $[M+H]^+$.

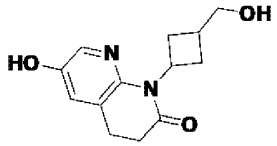
Step 3: 1-[3-(hydroxymethyl)cyclobutyl]-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



[1262] A mixture of 6-bromo-1-[3-(hydroxymethyl)cyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (900 mg, 2.89 mmol), KOAc (568 mg, 5.78 mmol), bis(pinacolato)diboron (808 mg, 3.18 mmol) and $Pd(dppf)Cl_2$ (236 mg, 0.289 mmol) in 1,4-dioxane (10 mL) was degassed and purged with N_2 (3x), and then stirred at 100 °C for 16 h under N_2 atmosphere. After cooling to room temperature, the reaction mixture was filtered and concentrated under in vacuo to give 1-[3-(hydroxymethyl)cyclobutyl]-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,8-

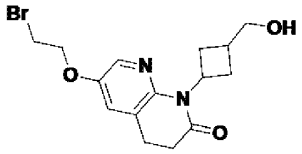
naphthyridin-2-one, which was taken onto the subsequent step without further purification. MS = 359.3 $[M+H]^+$.

Step 4: 6-hydroxy-1-[3-(hydroxymethyl)cyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



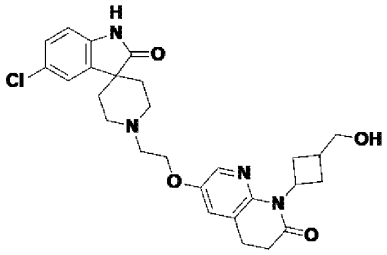
[1263] To a 0 °C solution of 1-[3-(hydroxymethyl)cyclobutyl]-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (800 mg, 1.67 mmol, 75% purity) in THF (10 mL) and H_2O (3 mL) was added Oxone (2.06 g, 3.35 mmol). The mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous Na_2SO_3 solution (10 mL) and extracted with EtOAc (3 x 10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–100% EtOAc/Petroleum ether) to give 6-hydroxy-1-[3-(hydroxymethyl)cyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one. MS = 249.0 $[M+H]^+$.

Step 5: 6-(2-bromoethoxy)-1-[3-(hydroxymethyl)cyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



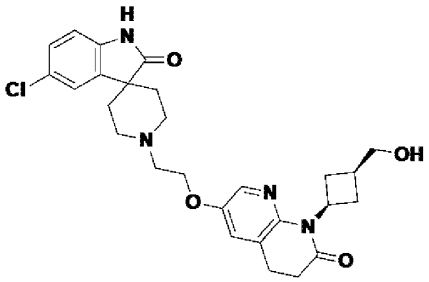
[1264] To a solution of 6-hydroxy-1-[3-(hydroxymethyl)cyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (300 mg, 1.21 mmol) in MeCN (2 mL) was added K_2CO_3 (334 mg, 2.42 mmol) and 1,2-dibromoethane (2.73 mL, 36.3 mmol). The mixture was stirred at 80 °C for 4 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo to remove MeCN. The residue was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 4 g cartridge, 0–100% EtOAc/Petroleum ether) to give 6-(2-bromoethoxy)-1-[3-(hydroxymethyl)cyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one. MS = 354.9 / 356.9 $[M+H]^+$.

Step 6: 5-chloro-1'-[2-({8-[3-(hydroxymethyl)cyclobutyl]-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one and (Compound 326)



[1265] To a solution of 6-(2-bromoethoxy)-1-[3-(hydroxymethyl)cyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (140 mg, 0.394 mmol) in MeCN (3 mL) was added $NaHCO_3$ (66.2 mg, 0.788 mmol) and 5-chloro-1H-spiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 129 mg, 0.473 mmol, HCl salt). The mixture was stirred at 80 °C for 4 h. After cooling to room temperature, the reaction mixture was filtered and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex C_{18} column, 25–45% MeCN with H_2O with 10 mM NH_4HCO_3 modifier) to give 5-chloro-1'-[2-({8-[3-(hydroxymethyl)cyclobutyl]-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one and (**Compound 326**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 1H), 7.99 – 7.90 (m, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.38 (d, J = 2.8 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 4.82 (t, J = 8.8 Hz, 1H), 4.55 – 4.28 (m, 1H), 4.18 (t, J = 5.6 Hz, 2H), 3.41 (d, J = 6.3 Hz, 2H), 2.92 (t, J = 11.2 Hz, 2H), 2.86 (t, J = 5.6 Hz, 2H), 2.80 (t, J = 7.2 Hz, 2H), 2.73 – 2.67 (m, 2H), 2.48 (s, 2H), 2.36 – 2.24 (m, 4H), 2.15 – 2.02 (m, 1H), 1.83 – 1.67 (m, 4H). MS = 511.1 $[M+H]^+$.

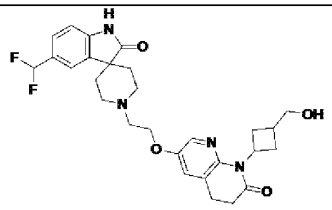
Step 7: 5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-(hydroxymethyl)cyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 327)

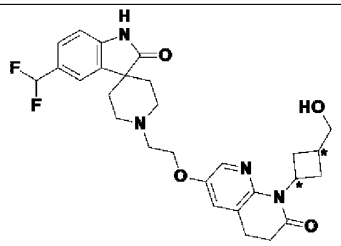
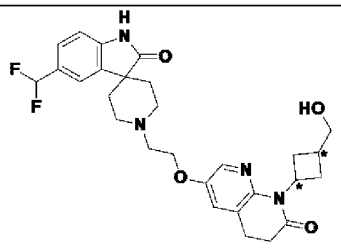
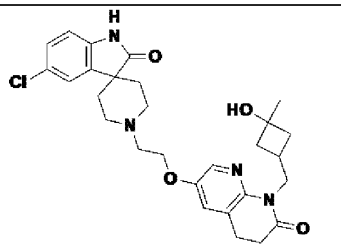


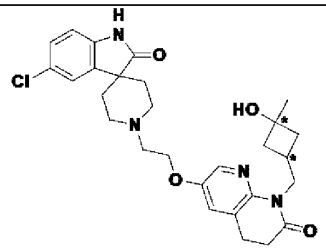
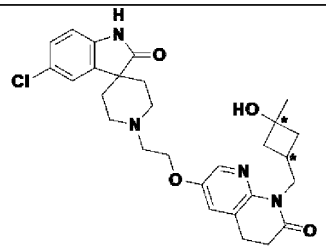
[1266] 5-chloro-1'-[2-({8-[3-(hydroxymethyl)cyclobutyl]-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one was separated by preparative chiral SFC (Daicel Chiralcel OX column, 60% MeOH with 0.1% NH_4OH in CO_2) to remove trace trans impurity. The first eluting diastereomer of the title compound, 5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-(hydroxymethyl)cyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 319**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 7.94 (d, J = 2.8 Hz, 1H), 7.50 (s, 1H), 7.38 (d, J = 2.4 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 4.83 (t, J = 8.8 Hz, 1H), 4.40 (t, J = 5.2 Hz, 1H), 4.18 (t, J = 5.6 Hz, 2H), 3.41 (t, J = 5.6 Hz, 2H), 2.92 (t, J = 7.2 Hz, 3H), 2.87 – 2.77 (m, 4H), 2.74 – 2.63 (m, 3H), 2.37 – 2.23 (m, 4H), 2.15 – 2.04 (m, 1H), 1.86 – 1.64 (m, 4H). MS = 511.2 $[M+H]^+$.

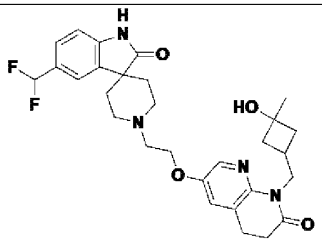
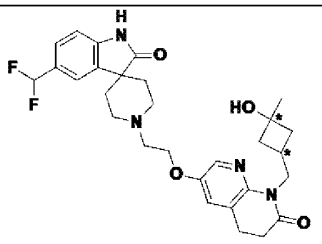
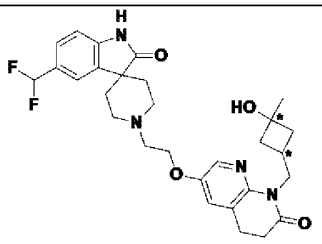
[1267] The following compounds in **Table 38.7** were prepared according to the procedures similar to those described for **Compounds 326 & 319** using the appropriate starting materials.

Table 38.7

No.	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Inter-mediate Used	Elution Order	Chi-ral Co-lumn
316		5-(difluoromethyl)-1'-[2-({8-[3-(hydroxymethyl)cyclobutyl]-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 527.2 Found 527.2	**B-1**	n/a	n/a

309		5-(difluoromethyl)-1'-[2-({7-oxo-8-*[(cis)* or *(trans)*-3-(hydroxymethyl)cyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 527.2 Found 527.3	**B-1**	1st	Daicel Chiralpak IG
310		5-(difluoromethyl)-1'-[2-({7-oxo-8-*[(trans)* or *(cis)*-3-(hydroxymethyl)cyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 527.2 Found 527.3	**B-1**	2nd	Daicel Chiralpak IG
327		5-chloro-1'-[2-({8-[(3-hydroxy-3-methylcyclobutyl)methyl]-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-	Calc'd 525.2 Found 525.1	**B-4** & **D-1**	n/a	n/a

		dihydrospiro[indole-3,4'-piperidin]-2-one				
313		5-chloro-1'-{2-[(7-oxo-8-{[*(cis)* or *(trans)*-3-hydroxy-3-methylcyclobutyl]methyl}-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 525.2 Found 525.3	**B-4** & **D-1**	1st	Chiralpak IE-3
322		5-chloro-1'-{2-[(7-oxo-8-{[(*trans)* or (*cis*)-3-hydroxy-3-methylcyclobutyl]methyl}-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 525.2 Found 525.3	**B-4** & **D-1**	2nd	Chiralpak IE-3

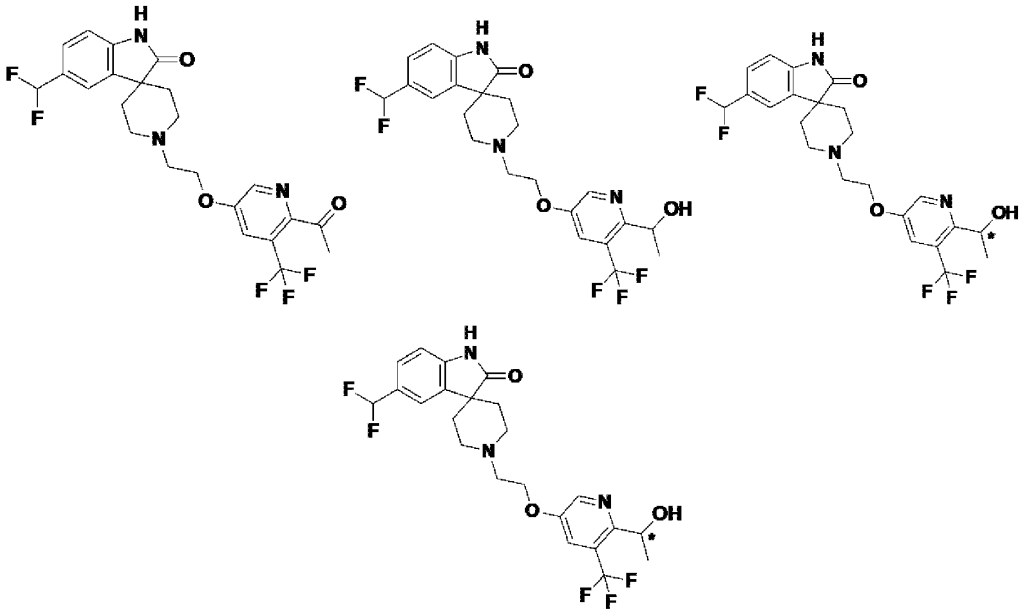
320		5-(difluoromethyl)-1'-[2-({8-[(3-hydroxy-3-methylcyclobutyl)methyl]-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 541.3 Found 541.3	**B-1** & **D-1**	n/a	n/a
311		5-(difluoromethyl)-1'-{2-[(7-oxo-8-*{[(cis)* or *(trans)*-3-hydroxy-3-methylcyclobutyl]methyl}-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 541.3 Found 541.1	**B-1** & **D-1**	1st	Chiralpak IE-3
312		5-(difluoromethyl)-1'-{2-[(7-oxo-8-*{[(trans)* or *(cis)*-3-hydroxy-3-methylcyclobutyl]methyl}-5,6,7,8-	Calc'd 541.3 Found 541.1	**B-1** & **D-1**	2nd	Chiralpak IE-3

		tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one				

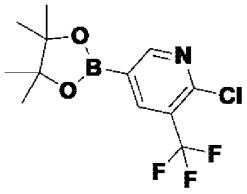
Example 71

1'-(2-{[6-acetyl-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-5-(difluoromethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 295), 5-(difluoromethyl)-1'-(2-{[6-(1-hydroxyethyl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 296), 5-(difluoromethyl)-1'-[2-({6-[(1*R*) or (1*S*)-1-hydroxyethyl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

(Compound 288), and 5-(difluoromethyl)-1'-[2-({6-[(1*S*) or (1*R*)-1-hydroxyethyl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 287)

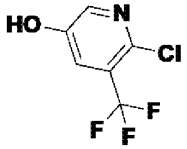


Step 1: 2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridine



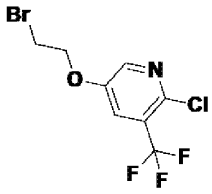
[1268] To a solution of 5-bromo-2-chloro-3-(trifluoromethyl)pyridine (5.00 g, 19.2 mmol) in 1,4-dioxane (70 mL) was added bis(pinacolato)diboron (6.83 g, 26.88 mmol), KOAc (4.71 g, 48.0 mmol), and $Pd(dppf)Cl_2$ (1.40 g, 1.92 mmol). The mixture was purged with N_2 (3x), and the mixture was stirred at 95 °C for 16 h under N_2 atmosphere. After cooling to room temperature, the reaction mixture was filtered, and the filter cake was washed with EtOAc. The filtrate was concentrated in vacuo to give 2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridine, which was used in the subsequent step without further purification.

Step 2: 6-chloro-5-(trifluoromethyl)pyridin-3-ol



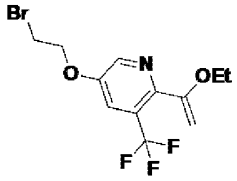
[1269] To a solution of 2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridine (5.00 g, 16.3 mmol) in THF (45 mL) and H_2O (15 mL) was added Oxone (10.00 g, 16.3 mmol). The mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with saturated aqueous Na_2SO_3 solution (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 80 g cartridge, 0–30% EtOAc/Petroleum ether) to give 6-chloro-5-(trifluoromethyl)pyridin-3-ol. MS = 197.9 $[M+H]^+$.

Step 3: 5-(2-bromoethoxy)-2-chloro-3-(trifluoromethyl)pyridine



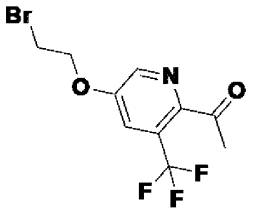
[1270] To a solution of 6-chloro-5-(trifluoromethyl)pyridin-3-ol (4.00 g, 20.3 mmol) in MeCN (20 mL) was added K_2CO_3 (14.0 g, 101 mmol) and 1,2-dibromoethane (15.3 mL, 202 mmol). The mixture was stirred at 70 °C for 10 h. After cooling to 0 °C, the reaction mixture was quenched with H_2O (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine (80 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 80 g cartridge, 0–12% EtOAc/Petroleum ether) to give 5-(2-bromoethoxy)-2-chloro-3-(trifluoromethyl)pyridine. MS = 303.8 / 305.8 $[M+H]^+$.

Step 4: 5-(2-bromoethoxy)-2-(1-ethoxyethenyl)-3-(trifluoromethyl)pyridine



[1271] To a solution of 5-(2-bromoethoxy)-2-chloro-3-(trifluoromethyl)pyridine (3.00 g, 9.85 mmol) in 1,4-dioxane (30 mL) was added tributyl(1-ethoxyvinyl)stannane (4.49 mL, 13.3 mmol) and $Pd(PPh_3)_2Cl_2$ (691 mg, 0.985 mmol). The mixture was degassed and purged with N_2 (3x) and stirred at 100 °C for 16 h. After cooling to room temperature, the mixture was quenched with saturated aqueous KF (50 mL) and stirred for 1 h. The mixture was filtered, and the filtrate was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 80 g cartridge, 0–30% EtOAc/Petroleum ether) to give 5-(2-bromoethoxy)-2-(1-ethoxyethenyl)-3-(trifluoromethyl)pyridine. MS = 340.1 / 342.0 $[M+H]^+$.

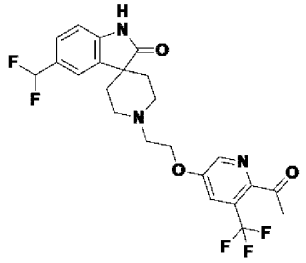
Step 5: 1-[5-(2-bromoethoxy)-3-(trifluoromethyl)pyridin-2-yl]ethan-1-one



[1272] To a 0 °C solution of 5-(2-bromoethoxy)-2-(1-ethoxyethenyl)-3-(trifluoromethyl)pyridine (3.00 g, 8.82 mmol) in THF (30 mL) was added 3.0 M aqueous HCl (30 mL, 90 mmol). The mixture was stirred at room temperature for 4 h. The mixture was adjusted to

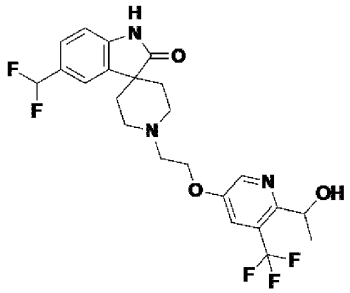
pH = 7–8 with saturated $NaHCO_3$ solution and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 40 g cartridge, 0–80% EtOAc/Petroleum ether) to give 1-[5-(2-bromoethoxy)-3-(trifluoromethyl)pyridin-2-yl]ethan-1-one. MS= 312.0 / 314.0 $[M+H]^+$.

Step 6: 1'-(2-{[6-acetyl-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-5-(difluoromethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 295)



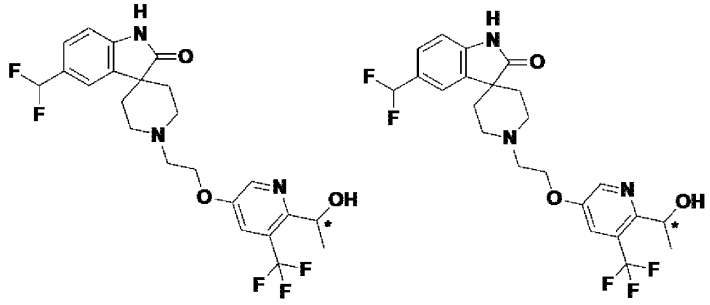
[1273] To a solution of 1-[5-(2-bromoethoxy)-3-(trifluoromethyl)pyridin-2-yl]ethan-1-one (500 mg, 1.60 mmol) and 5-(difluoromethyl)spiro[indoline-3,4'-piperidine]-2-one (**Intermediate B-1**, 509 mg, 1.76 mmol, HCl salt) in MeCN (10 mL) was added $NaHCO_3$ (673 mg, 8.01 mmol). The mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the mixture was filtered, and filtrate was concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex Luna C_{18} column, 5–40% MeCN with H_2O with 0.04% HCl modifier) to give 1'-(2-{[6-acetyl-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-5-(difluoromethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 295**, HCl salt). MS = 484.1 $[M+H]^+$.

Step 7: 5-(difluoromethyl)-1'-(2-{[6-(1-hydroxyethyl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 296)



[1274] To a 0 °C solution of 1'-(2-{[6-acetyl-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-5-(difluoromethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 295**, 700 mg, 1.45 mmol) in THF (10 mL) was added $NaBH_4$ (110 mg, 2.91 mmol). The mixture was stirred at room temperature for 3 h. The mixture was quenched with the dropwise addition of H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters Xbridge OBD C_{18} column, 30–70% MeCN:10 mM NH_4HCO_3 in H_2O) to give 5-(difluoromethyl)-1'-(2-{[6-(1-hydroxyethyl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 296**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.62 (s, 1H), 8.61 – 8.60 (m, 1H), 7.69 – 7.65 (m, 2H), 7.42 (d, J = 8.0 Hz, 1H), 7.09 – 7.81 (m, 2H), 5.12 (d, J = 6.8 Hz, 1H), 4.98 – 4.95 (m, 1H), 4.34 (t, J = 5.6 Hz, 2H), 2.96 – 2.93 (m, 2H), 2.90 – 2.87 (m, 2H), 2.72 – 2.70 (m, 2H), 1.82 – 1.80 (m, 2H), 1.69 – 1.67 (m, 2H), 1.38 (d, J = 6.4 Hz, 3H). MS= 486.1 $[M+H]^+$.

Step 8: 5-(difluoromethyl)-1'-[2-({6-[(1*R*) or (1*S*)-1-hydroxyethyl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 288) and 5-(difluoromethyl)-1'-[2-({6-[(1*S*) or (1*R*)-1-hydroxyethyl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 287)



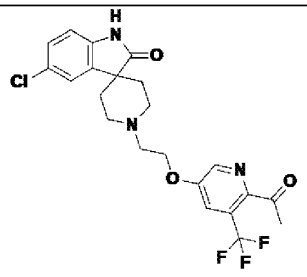
[1275] 5-(difluoromethyl)-1'-(2-{[6-(1-hydroxyethyl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 296**) was separated by preparative chiral SFC (Daicel Chiralpak IG-3 column, 50% EtOH with 0.1% NH_4OH in CO_2). The first eluting enantiomer of the title compound, 5-(difluoromethyl)-1'-[2-({6-[(1*R*) or (1*S*)-1-hydroxyethyl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 288**). The second eluting enantiomer of the title compound, 5-(difluoromethyl)-1'-

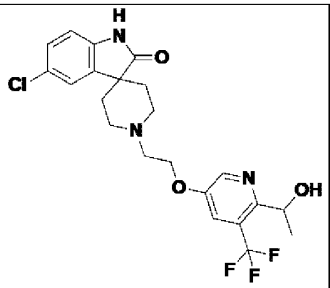
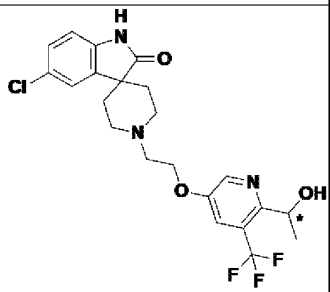
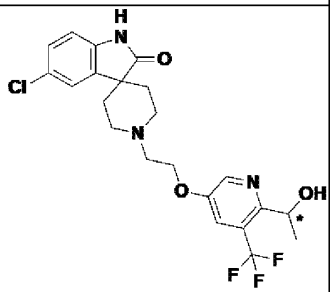
[2-({6-[(1*S*) or (1*R*)-1-hydroxyethyl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 287**).

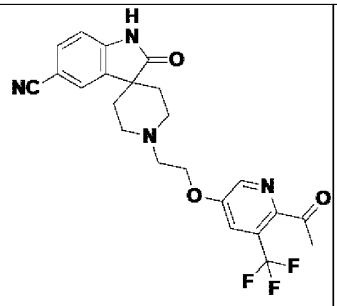
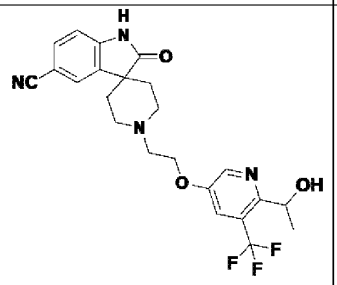
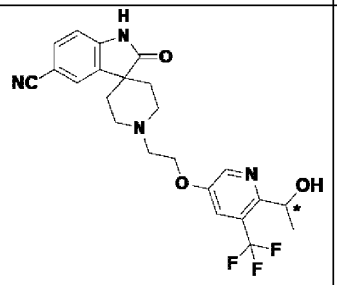
[1276] 5-(difluoromethyl)-1'-[2-({6-[(1*R*) or (1*S*)-1-hydroxyethyl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 288**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.62 (s, 1H), 8.61 – 8.60 (m, 1H), 7.68 (s, 1H), 7.65 (s, 1H), 7.43 – 7.41 (m, 1H), 7.09 – 6.81 (m, 2H), 5.12 (d, J = 7.6 Hz, 1H), 4.96 (t, J = 6.4 Hz, 1H), 4.34 (t, J = 5.6 Hz, 2H), 2.95 – 2.93 (m, 2H), 2.90 – 2.87 (m, 2H), 2.72 – 2.70 (m, 2H), 1.82 – 1.80 (m, 2H), 1.69 – 1.67 (m, 2H), 1.38 (d, J = 6.8 Hz, 3H). MS = 486.1 $[M+H]^+$. 5-(difluoromethyl)-1'-[2-({6-[(1*S*) or (1*R*)-1-hydroxyethyl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 287**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.62 (s, 1H), 8.61 – 8.60 (m, 1H), 7.68 (s, 1H), 7.65 (s, 1H), 7.43 – 7.41 (m, 1H), 6.97 – 6.81 (m, 2H), 5.12 (d, J = 6.8 Hz, 1H), 4.96 – 4.95 (m, 1H), 4.34 (t, J = 5.6 Hz, 2H), 2.95 – 2.93 (m, 2H), 2.90 – 2.87 (m, 2H), 2.72 – 2.70 (m, 2H), 1.82 – 1.80 (m, 2H), 1.69 – 1.67 (m, 2H), 1.38 (d, J = 6.8 Hz, 3H). MS = 486.1 $[M+H]^+$.

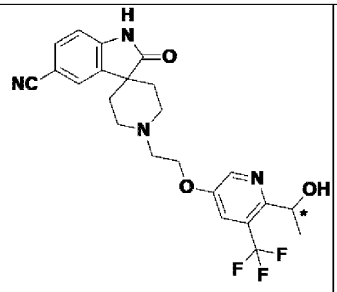
[1277] The following compounds in **Table 38.8** were prepared according to the procedures similar to those described for **Compounds 295, 296, 287, & 288** using the appropriate starting materials.

Table 38.8

No.	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Inter-mediate Used	Elu-tion Order	Chi-ral Col-umn
294		1'-(2-{[6-acetyl-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 468.1 Found 468.1	**B-4**	n/a	n/a

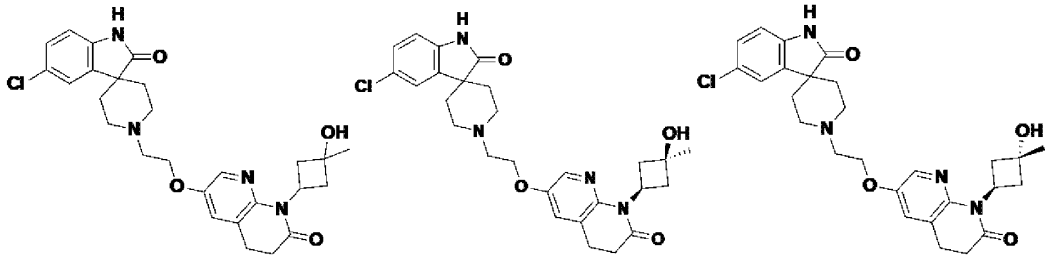
399		5-chloro-1'-(2-{[6-(1-hydroxyethyl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 470.1 Found 470.2	**B-4**	n/a	n/a
292		5-chloro-1'-[2-({6-[(1*S*) or (1*R*)-1-hydroxyethyl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 470.1 Found 470.1	**B-4**	1st	Daicel Chiralpak IG-3
291		5-chloro-1'-[2-({6-[(1*R*) or (1*S*)-1-hydroxyethyl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 470.1 Found 470.1	**B-4**	2nd	Daicel Chiralpak IG-3

298		1'-(2-{[6-acetyl-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 459.2 Found 459.2	**B-9**	n/a	n/a
338		1'-(2-{[6-(1-hydroxyethyl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 461.2 Found 461.3	**B-9**	n/a	n/a
376		1'-[2-({6-[(1*S*) or (1*R*)-1-hydroxyethyl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 461.2 Found 461.1	**B-9**	1st	Daicel Chiralpak IG-3

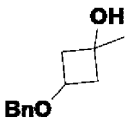
377		1'-[2-({6-[(1*S*) or (1*R*)-1-hydroxyethyl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 461.2 Found 461.1	**B-9**	2nd	Daicel Chiralpak IG-3

Example 72

5-chloro-1'-(2-{[8-(3-hydroxy-3-methylcyclobutyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 315), 5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 275), and 5-chloro-1'-[2-({7-oxo-8-[(*trans*)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 307)



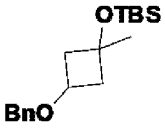
Step 1: 3-(benzyloxy)-1-methylcyclobutan-1-ol



[1278] To a –20 °C solution of 3.0 M MeMgBr in 2-MeTHF (94 mL, 282 mmol) in THF (1.0 L) under N_2 atmosphere was added a solution of 3-(benzyloxy)cyclobutan-1-one (25.0 g, 142 mmol) in

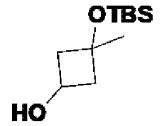
THF (200 mL) dropwise. The mixture was stirred at –20°C for 30 min. The mixture was warmed to 0 °C, quenched with H_2O (300 mL), and stirred at 0 °C for 15 min. The mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give 3-(benzyloxy)-1-methylcyclobutan-1-ol, which was used in the subsequent step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.31 (m, 5H), 4.45 (s, 3H), 3.75 – 3.72 (m, 1H), 2.48 – 2.43 (m, 2H), 2.13 – 2.09 (m, 2H), 1.32 (s, 3H).

Step 2: [3-(benzyloxy)-1-methylcyclobutoxy](*tert*-butyl)dimethylsilane



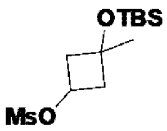
[1279] To a solution of 3-benzyloxy-1-methyl-cyclobutanol (30 g, 156 mmol) in DCM (300 mL) was added imidazole (32.0 g, 468 mmol) and TBSCl (28.7 mL, 234 mmol). The mixture was stirred at room temperature for 16 h. The mixture was filtered, and filtrate was in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 330 g cartridge, 0–5% EtOAc/Petroleum ether) to give [3-(benzyloxy)-1-methylcyclobutoxy](*tert*-butyl)dimethylsilane. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.34 – 7.29 (m, 5H), 4.42 (s, 2H), 3.70 – 3.65 (m, 1H), 2.42 – 2.38 (m, 2H), 2.19 – 2.17 (m, 2H), 1.30 (s, 3H), 0.90 (s, 9H), 0.09 (s, 6H).

Step 3: 3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutan-1-ol



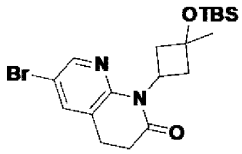
[1280] To a solution of [3-(benzyloxy)-1-methylcyclobutoxy](*tert*-butyl)dimethylsilane (49.0 g, 160 mmol) in MeOH (1.5 L) under N_2 atmosphere was added Pd/C (20.0 g, 10 wt%, 18.9 mmol). The mixture was degassed and purged with H_2 (3x). The mixture was stirred at 40 °C for 16 h under H_2 (15 psi). After cooling to room temperature, the mixture was filtered, and filtrate was concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 330 g cartridge, 0–30% EtOAc/Petroleum ether) to give 3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutan-1-ol.

Step 4: 3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl methanesulfonate



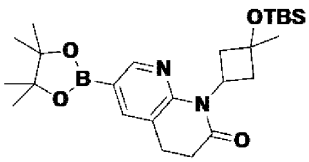
[1281] To a 0 °C solution of 3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutan-1-ol (10.0 g, 46.2 mmol) in DCM (100 mL) was added TEA (12.9 mL, 92.4 mmol). Methanesulfonic anhydride (12.1 g, 69.3 mmol) was added, and the mixture was stirred at room temperature for 16 h. The mixture was poured into ice water (100 ml) and extracted with DCM (3 x 100 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide 3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl methanesulfonate, which was used in the subsequent step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.75 – 4.68 (m, 1H), 3.33 (s, 3H), 2.59 – 2.54 (m, 2H), 2.25 – 2.24 (m, 2H), 1.30 (s, 3H), 0.85 (s, 9H), 0.07 (s, 6H).

Step 5: 6-bromo-1-{3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl}-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



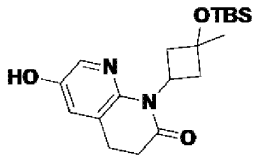
[1282] To a solution of 6-bromo-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (1.20 g, 5.29 mmol) and 3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl methanesulfonate (6.23 g, 21.1 mmol) in DMSO (100 mL) was added Cs_2CO_3 (5.17 g, 15.9 mmol). The mixture was stirred at 130 °C for 16 h. The mixture was poured into H_2O (100 ml) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 120 g cartridge, 0–30% EtOAc/Petroleum ether) to give 6-bromo-1-{3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl}-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one. MS = 425.1 / 427.1 $[M+H]^+$.

Step 6: 1-{3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl}-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



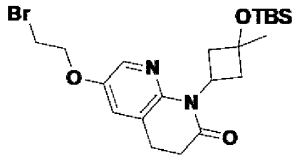
[1283] To a solution of 6-bromo-1-{3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl}-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (5.00 g, 11.8 mmol) in 1,4-dioxane (100 mL) was added AcOK (2.31 g, 23.5 mmol) and bis(pinacolato)diboron (3.58 g, 14.1 mmol). $Pd(dppf)Cl_2$ (860 mg, 1.18 mmol) was added, and the mixture was degassed and purged with N_2 (3x). The mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the mixture was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 80 g cartridge, 0–40% EtOAc/Petroleum ether) to give 1-{3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl}-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one. MS = 473.4 $[M+H]^+$.

Step 7: 1-{3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl}-6-hydroxy-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



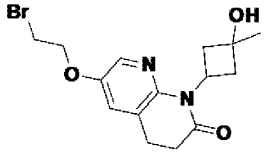
[1284] To a 0 °C solution of 1-{3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl}-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (7.00 g, 14.8 mmol) in THF (90 mL) and H_2O (30 mL) was added Oxone (13.7 g, 22.2 mmol). The mixture was stirred at room temperature for 3 h. The mixture was poured into ice water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 80 g cartridge, 0–40% EtOAc/Petroleum ether) to give 1-{3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl}-6-hydroxy-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one. MS = 363.2 $[M+H]^+$.

Step 8: 6-(2-bromoethoxy)-1-{3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl}-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



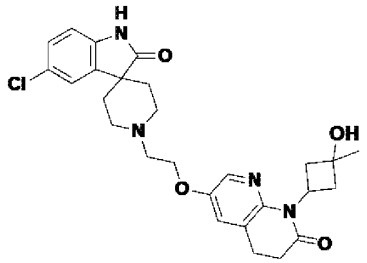
[1285] To a solution of 1-{3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl}-6-hydroxy-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (1.30 g, 3.59 mmol) and 1,2-dibromoethane (8.12 mL, 108 mmol) in MeCN (1.0 mL) was added K_2CO_3 (1.49 g, 10.8 mmol). The mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the mixture was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–80% EtOAc/Petroleum ether) to give 6-(2-bromoethoxy)-1-{3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl}-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one. MS = 469.2 / 471.2 $[M+H]^+$.

Step 9: 6-(2-bromoethoxy)-1-(3-hydroxy-3-methylcyclobutyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



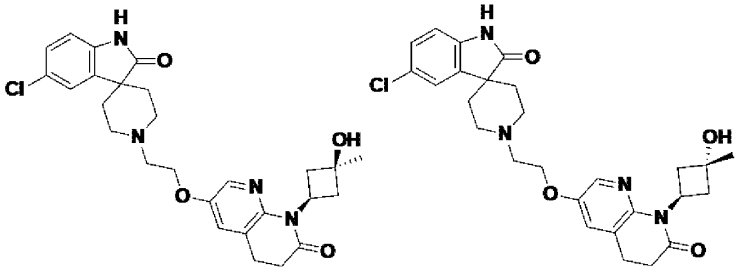
[1286] To a 0 °C solution of 6-(2-bromoethoxy)-1-{3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl}-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (1.00 g, 2.13 mmol) in THF (2 mL) was added 6.0 M HCl in H_2O (8 mL, 48 mmol). The mixture was stirred at room temperature for 2 h, then was concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–80% EtOAc/Petroleum ether) to give 6-(2-bromoethoxy)-1-(3-hydroxy-3-methylcyclobutyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one. MS = 355.1 / 357.1 $[M+H]^+$.

Step 10: 5-chloro-1'-(2-{[8-(3-hydroxy-3-methylcyclobutyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 315)



[1287] To a solution of 6-(2-bromoethoxy)-1-(3-hydroxy-3-methylcyclobutyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (200 mg, 0.563 mmol) and 5-chloro-1H-spiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 231 mg, 0.845 mmol, HCl salt) in MeCN (5.0 mL) was added $NaHCO_3$ (331 mg, 3.94 mmol). The mixture was stirred at 80 °C for 16 h. The mixture was filtered, and filtrate was concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex Luna C_{18} column, 5–35% MeCN with H_2O with 0.04% HCl modifier) to give 5-chloro-1'-(2-{[8-(3-hydroxy-3-methylcyclobutyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 315**, HCl salt). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.20 – 11.17 (m, 0.5H), 10.81 – 10.73 (m, 1H), 10.63 (s, 0.5H), 8.03 – 8.00 (m, 1.5H), 7.45 (s, 1H), 7.30 – 7.28 (m, 1H), 7.15 (s, 0.5H), 6.94 – 6.89 (m, 1H), 5.34 – 5.25 (m, 1H), 4.51 (s, 2H), 3.83 (s, 1H), 3.82 – 3.66 (m, 4H), 3.64 (s, 1H), 2.84 – 2.80 (m, 2H), 2.66 – 2.65 (m, 2H), 2.64 – 2.53 (m, 3H), 2.24 – 2.18 (m, 3H), 2.18 – 1.94 (m, 2H), 1.31 (s, 3H). MS = 511.2 $[M+H]^+$.

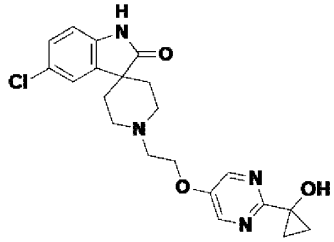
Step 11: 5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 275) and 5-chloro-1'-[2-({7-oxo-8-[(*trans*)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 307)



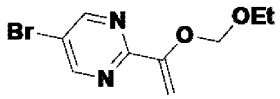
[1288] 5-chloro-1'-(2-{[8-(3-hydroxy-3-methylcyclobutyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 315**) was separated by preparative chiral SFC (Daicel Chiralpak AD-3 column, 50% IPA with 0.1% NH_4OH in CO_2). The first eluting diastereomer of the title compound, 5-chloro-1'-[2-({7-oxo-8-[(*trans*)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 307**). The second eluting diastereomer of the title compound, 5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 275**, **Example 59**). 5-chloro-1'-[2-({7-oxo-8-[(*trans*)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 307**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 7.96 (s, 1H), 7.50 – 7.49 (m, 1H), 7.38 – 7.37 (m, 1H), 7.25 – 7.22 (m, 1H), 6.85 – 6.83 (m, 1H), 5.32– 5.27 (m, 1H), 4.78 (s, 1H), 4.19 – 4.17 (m, 2H), 2.92 – 2.78 (m, 2H), 2.69 – 2.67 (m, 4H), 2.66 – 2.52 (m, 4H), 2.40 – 2.20 (m, 2H), 2.19 – 2.18 (m, 2H), 1.78 – 1.72 (m, 4H), 1.30 (s, 3H). MS= 511.2 $[M+H]^+$.

Example 73

5-chloro-1'-(2-{[2-(1-hydroxycyclopropyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 308)



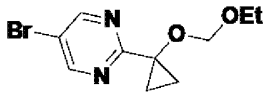
Step 1: 5-bromo-2-[1-(ethoxymethoxy)ethenyl]pyrimidine



[1289] To a three-neck round-bottom flask equipped with a magnetic stir bar and thermometer under N_2 atmosphere was added 1-(5-bromopyrimidin-2-yl)ethan-1-one (5.00 g, 24.9 mmol) and THF (80 mL). The mixture was cooled to –78 °C and then 1.0 M LiHMDS in hexane (37.3 mL, 37.3 mmol) was added dropwise over 5 min. After stirring for 10 min, chloromethoxyethane (2.77 mL,

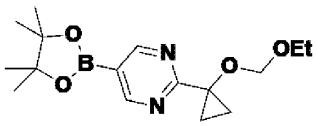
29.9 mmol) was added dropwise. The mixture was slowly warmed to room temperature and stirred for another 5 h. After cooling to 0 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl (80 mL), and then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 80 g cartridge, 0–20% EtOAc/Petroleum ether) to give 5-bromo-2-[1-(ethoxymethoxy)ethenyl]pyrimidine. MS= 259.1 / 261.0 $[M+H]^+$.

Step 2: 5-bromo-2-[1-(ethoxymethoxy)cyclopropyl]pyrimidine



[1290] To a solution of trimethylsulfoxonium iodide (4.08 g, 18.5 mmol) in DMSO (10 mL) was added *t*-BuOK (1.82 g, 16.2 mmol). The mixture was stirred at 50 °C for 30 min, and then a solution of 5-bromo-2-[1-(ethoxymethoxy)vinyl]pyrimidine (1.20 g, 4.63 mmol) in DMSO (10 mL) was added dropwise. The mixture was stirred at 50 °C for 30 min. After cooling to 0 °C, the reaction mixture was quenched with H_2O (20 mL), and then extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 20 g cartridge, 0–20% EtOAc/Petroleum ether) to give 5-bromo-2-[1-(ethoxymethoxy)cyclopropyl]pyrimidine, MS = 273.1 / 275.1 $[M+H]^+$.

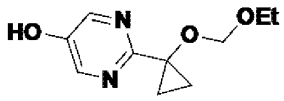
Step 3: 2-[1-(ethoxymethoxy)cyclopropyl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine



[1291] A mixture of 5-bromo-2-[1-(ethoxymethoxy)cyclopropyl]pyrimidine (570 mg, 2.09 mmol), bis(pinacolato)diboron (795 mg, 3.13 mmol), KOAc (614 mg, 6.26 mmol), and $Pd(dppf)Cl_2$ (76.4 mg, 0.104 mmol) in 1,4-dioxane (15 mL) was degassed and purged with N_2 (3x), and then the mixture was stirred at 80 °C for 15 h under N_2 atmosphere. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated in vacuo to give 2-[1-

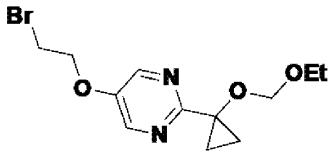
(ethoxymethoxy)cyclopropyl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine, which was used in the subsequent step without further purification.

Step 4: 2-[1-(ethoxymethoxy)cyclopropyl]pyrimidin-5-ol



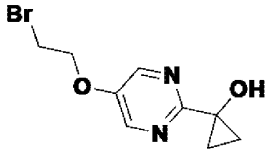
[1292] To a solution of 2-[1-(ethoxymethoxy)cyclopropyl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (700 mg, 2.19 mmol) in MeCN (15 mL) and H_2O (15 mL) was added Oxone (2.02 g, 3.28 mmol). The mixture was stirred for 2 h. The reaction mixture was quenched with saturated aqueous Na_2SO_3 (10 mL) at 0°C, and then extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–50% EtOAc/Petroleum ether) to give 2-[1-(ethoxymethoxy)cyclopropyl]pyrimidin-5-ol. MS= 211.3 $[M+H]^+$.

Step 5: 5-(2-bromoethoxy)-2-[1-(ethoxymethoxy)cyclopropyl]pyrimidine



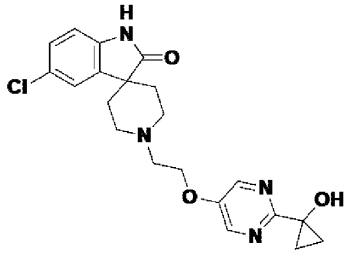
[1293] To a solution of 2-[1-(ethoxymethoxy)cyclopropyl]pyrimidin-5-ol (600 mg, 2.85 mmol) and 1,2-dibromoethane (8.61 mL, 114 mmol) in MeCN (10 mL) was added K_2CO_3 (1.97 g, 14.3 mmol). The mixture was stirred at 65 °C for 5 h. After cooling to room temperature, the mixture was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–35% EtOAc/Petroleum ether) to give 5-(2-bromoethoxy)-2-[1-(ethoxymethoxy)cyclopropyl]pyrimidine. MS= 317.2 / 319.1 $[M+H]^+$.

Step 6: 1-[5-(2-bromoethoxy)pyrimidin-2-yl]cyclopropan-1-ol



[1294] To a solution of 5-(2-bromoethoxy)-2-[1-(ethoxymethoxy)cyclopropyl]pyrimidine (300 mg, 0.946 mmol) in DCM (15 mL) was added TFA (1.0 mL). The mixture was stirred for 1 h, then was concentrated in vacuo. The residue was cooled to 0 °C and quenched with H_2O (15 mL), and then adjusted to pH = 8 with saturated aqueous $NaHCO_3$. The biphasic mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give 5-(2-bromoethoxy)-2-[1-(ethoxymethoxy)cyclopropyl]pyrimidine. MS = 259.0 / 261.0 $[M+H]^+$.

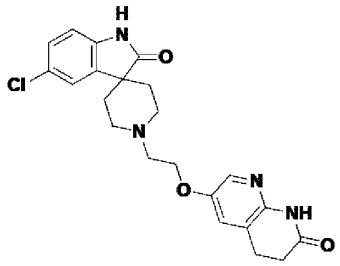
Step 7: 5-chloro-1'-(2-{[2-(1-hydroxycyclopropyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 308)



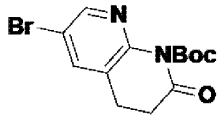
[1295] A mixture of 1-[5-(2-bromoethoxy)pyrimidin-2-yl]cyclopropanol (100 mg, 0.386 mmol), 5-chloro-1H-spiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 111 mg, 0.405 mmol, HCl salt), and $NaHCO_3$ (162 mg, 1.93 mmol) in MeCN (4 mL) was degassed and purged with N_2 (3x), and then the mixture was stirred at 80 °C for 15 h under N_2 atmosphere. After cooling to room temperature, the mixture was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex Kinetex C_{18} column, 15–45% MeCN with H_2O with 0.1% NH_4OH modifier) to give 5-chloro-1'-(2-{[2-(1-hydroxycyclopropyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 308**). ^1H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 8.49 (s, 2H), 7.50 (d, J = 2.0 Hz, 1H), 7.23 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 5.90 (s, 1H), 4.28 (t, J = 5.6 Hz, 2H), 2.93 – 2.85 (m, 4H), 2.71 – 2.69 (m, 2H), 1.78 – 1.72 (m, 4H), 1.21 – 1.18 (m, 2H), 1.09 – 1.06 (m, 2H). MS = 415.1 $[M+H]^+$.

Example 74

5-chloro-1'-{2-[(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 293)

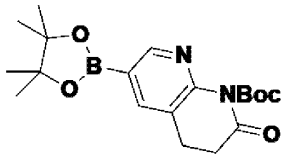


Step 1: *tert*-butyl 6-bromo-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridine-1-carboxylate



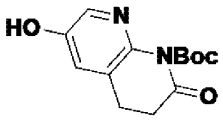
[1296] To a solution of 6-bromo-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (10.0 g, 44.0 mmol) in DCM (70 mL) was added Boc_2O (12.1 mL, 52.9 mmol), DIEA (11.5 mL, 66.1 mmol) and DMAP (538 mg, 4.40 mmol). The mixture was stirred for 4 h, then solids were removed by filtration. The filtrate was diluted with H_2O (80 mL) and extracted with EtOAc (2 x 60 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 80 g cartridge, 0–35% EtOAc/Petroleum ether) to give *tert*-butyl 6-bromo-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridine-1-carboxylate.

Step 2: *tert*-butyl 2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,8-naphthyridine-1-carboxylate



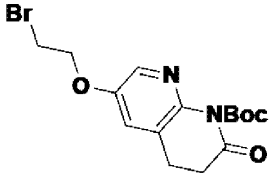
[1297] A mixture of *tert*-butyl 6-bromo-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridine-1-carboxylate (3.00 g, 9.17 mmol), bis(pinacolato)diboron (2.79 g, 11.0 mmol), KOAc (2.25 g, 22.9 mmol), and $Pd(dppf)Cl_2$ (67.1 mg, 91.7 μmol) in 1,4-dioxane (30 mL) was degassed and purged with N_2 (3x), and then the mixture was stirred at 90 °C for 12 h under N_2 atmosphere. After cooling to room temperature, the mixture was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 25 g cartridge, 0–100% EtOAc/Petroleum ether) to give *tert*-butyl 2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,8-naphthyridine-1-carboxylate. MS = 375.3 $[M+H]^+$.

Step 3: *tert*-butyl 6-hydroxy-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridine-1-carboxylate



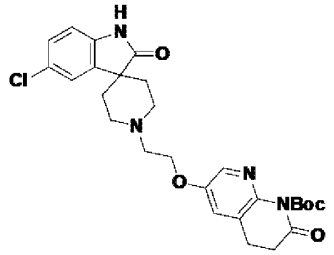
[1298] To a solution of *tert*-butyl 2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,8-naphthyridine-1-carboxylate (1.00 g, 2.67 mmol) in H_2O (2 mL) and THF (10 mL) was added Oxone (1.15 g, 1.87 mmol). The mixture was stirred at 0 °C for 1 h, and then was quenched with saturated aqueous Na_2SO_3 (10 mL). The mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give *tert*-butyl 6-hydroxy-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridine-1-carboxylate, which was used in the subsequent step without further purification. MS = 265.1 $[M+H]^+$.

Step 4: *tert*-butyl 6-(2-bromoethoxy)-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridine-1-carboxylate



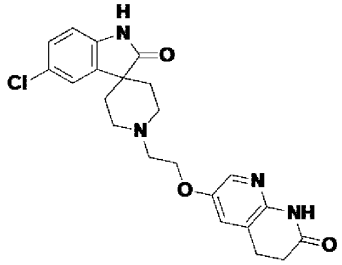
[1299] To a solution of *tert*-butyl 6-hydroxy-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridine-1-carboxylate (900 mg, 3.41 mmol) in MeCN (7 mL) and 1,2-dibromoethane (16 mL) was added K_2CO_3 (2.35 g, 17.0 mmol). The mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 4 g cartridge, 0–50% EtOAc/Petroleum ether) to give *tert*-butyl 6-(2-bromoethoxy)-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridine-1-carboxylate. MS = 371.1 / 373.1$[M+H]^+$.

Step 5: *tert*-butyl 6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridine-1-carboxylate



[1300] To a solution of 5-chloro-1H-spiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 515 mg, 1.89 mmol, HCl salt) in MeCN (10 mL) was added $NaHCO_3$ (634 mg, 7.54 mmol) and *tert*-butyl 6-(2-bromoethoxy)-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridine-1-carboxylate (700 mg, 1.89 mmol). The mixture was stirred at 80 °C for 12 h. After cooling to room temperature, the reaction mixture was filtered and concentrated in vacuo. The residue was purified by preparative TLC (SiO_2, 100% EtOAc) to give *tert*-butyl 6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridine-1-carboxylate. MS = 527.0 $[M+H]^+$.

Step 6: 5-chloro-1'-{2-[(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 293)

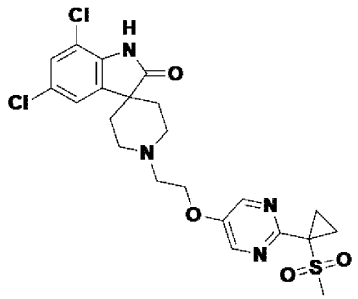


[1301] A mixture of *tert*-butyl 6-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridine-1-carboxylate (330 mg, 0.626 mmol) in 4.0 M HCl in EtOAc (10 mL, 40 mmol) was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by reverse phase preparative HPLC (Waters Xbridge BEH C_{18} column, 20–50% MeCN:10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-{2-[(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one **(Compound 293)**. ^1H NMR (400 MHz, DMSO-d_6): δ 9.67 (s, 1H), 9.46 (s, 1H), 7.02 (d, J = 2.8 Hz, 1H), 6.69 (d, J = 2.0 Hz, 1H), 6.53 (d, J = 2.6 Hz,

1H), 6.42 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 6.03 (d, J = 8.4 Hz, 1H), 3.33 (t, J = 5.6 Hz, 2H), 1.98 – 2.17 (m, 6H), 1.87 – 1.82 (m, 2H), 1.66 – 1.57 (m, 2H), 0.99 – 0.90 (m, 4H). MS = 427.2 $[M+H]^+$.

Example 75

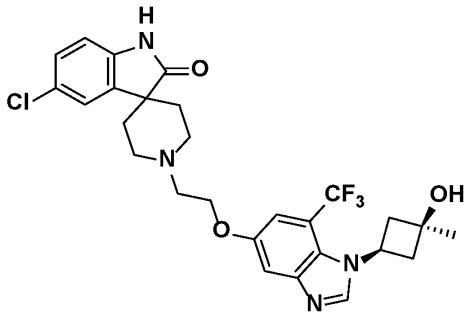
5,7-dichloro-1'-(2-{[2-(1-methanesulfonylcyclopropyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 400)



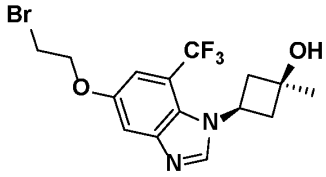
[1302] To a solution of 5-chloro-1'-(2-{[2-(1-methanesulfonylcyclopropyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 4**, 100 mg, 0.21 mmol) and NCS (0.056 g, 0.419 mmol) in MeCN (0.5 mL) was added TMSCl (0.023 g, 0.21 mmol). The reaction was allowed to stir at room temperature overnight. The reaction was diluted with H_2O (1 mL) and DMSO (1 mL), and then purified by reverse phase C18 chromatography (5–50% MeCN in H_2O with 0.1% NH_4OH modifier) to give 5,7-dichloro-1'-(2-{[2-(1-methanesulfonylcyclopropyl)pyrimidin-5-yl]oxy}ethyl)-1H-spiro[indole-3,4'-piperidin]-2-one (**Compound 400**). ^{1}H NMR (500 MHz, DMSO): δ 10.87 (s, 1H), 8.54 (s, 2H), 7.45 (s, 1H), 7.36 (s, 1H), 4.26 (t, J = 5.6 Hz, 2H), 3.29 (s, 3H), 2.86 – 2.78 (m, 4H), 2.66 – 2.61 (m, 2H), 1.72 – 1.65 (m, 6H), 1.54 – 1.51 (m, 2H). MS = 511.1 $[M+H]^+$.

Example 76

5-chloro-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 352)

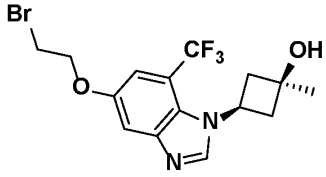


Step 1: (*cis*)-3-[5-(2-bromoethoxy)-7-(trifluoromethyl)-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol



[1303] To a solution of 1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-ol (**Intermediate A-92**, 610 mg, 2.13 mmol) in MeCN (12.2 mL) was added K_2CO_3 (1.47 g, 10.7 mmol) and 1,2-dibromoethane (16.0 g, 85.2 mmol). The mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was quenched by addition of H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–30% MeOH/EtOAc) to give (*cis*)-3-[5-(2-bromoethoxy)-7-(trifluoromethyl)-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol. MS = 393.0 / 395.0 $[M+H]^+$.

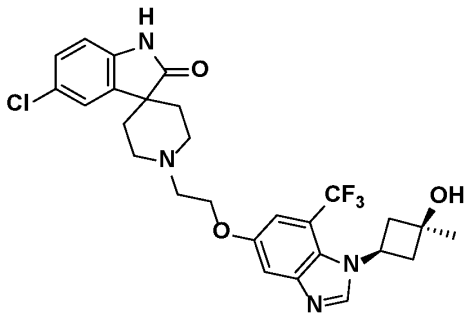
Alternative Conditions for Step 1: (*cis*)-3-[5-(2-bromoethoxy)-7-(trifluoromethyl)-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol



[1304] A solution of 1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-ol (**Intermediate A-92**, 1.00 g, 3.49 mmol), 1,2-dibromoethane (5.27 mL, 69.9

mmol) and Cs_2CO_3 (2.85 g, 8.73 mmol) in *i*-PrOH (5 mL) was stirred at 60 °C for 16 h. After cooling to room temperature, solids were removed by filtration and the filtrate was concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 20 g cartridge, 50–90% EtOAc/Petroleum ether) to give (*cis*)-3-[5-(2-bromoethoxy)-7-(trifluoromethyl)-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol. MS = 393.0 / 394.9 $[M+H]^+$.

Step 2: 5-chloro-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

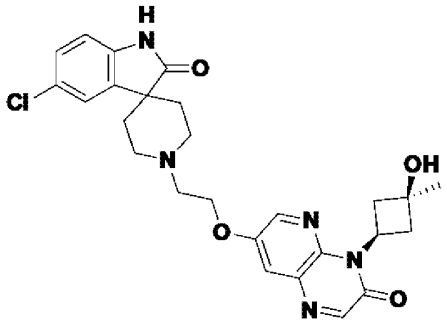


[1305] To a solution of (*cis*)-3-[5-(2-bromoethoxy)-7-(trifluoromethyl)-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol (420 mg, 1.07 mmol) in MeCN (7 mL) was added $NaHCO_3$ (449 mg, 5.34 mmol) and 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 321 mg, 1.17 mmol, HCl salt). The mixture was stirred at 80 °C for 12 h. After cooling to room temperature, the reaction mixture was quenched by addition of H_2O (20 mL) and extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was suspended in MeCN (10 mL) and the mixture was stirred at 80 °C for 1 h. The mixture was cooled to room temperature and filtered to collect the solid. The filter cake was dried in vacuo to give 5-chloro-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 352**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 8.67 (s, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.26 – 7.21 (m, 2H), 6.83 (d, J = 8.4 Hz, 1H), 5.30 (s, 1H), 4.57 (pent, J = 8.0 Hz, 1H), 4.26 – 4.23 (m, 2H), 2.93 – 2.87 (m, 4H), 2.72 – 2.62 (m, 2H), 2.60 – 2.50 (m, 4H), 1.79 – 1.68 (m, 4H), 1.33 (s, 3H). MS = 549.0 $[M+H]^+$.

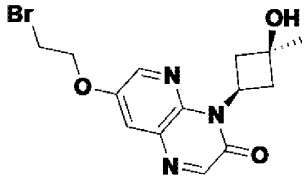
Example 77

5-chloro-1'-[2-({3-oxo-4-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-3H,4H-pyrido[2,3-b]pyrazin-7-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

(Compound 358)

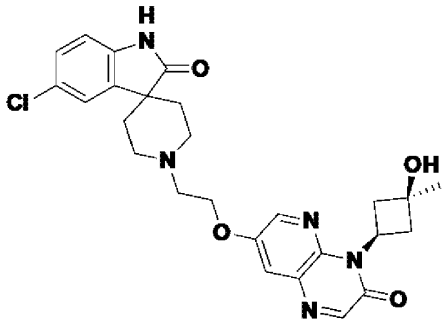


Step 1: 7-(2-bromoethoxy)-4-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-3H,4H-pyrido[2,3-b]pyrazin-3-one



[1306] To a solution of 7-hydroxy-4-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-3H,4H-pyrido[2,3-b]pyrazin-3-one (**Intermediate A-94,** 140 mg, 0.388 mmol, TFA salt) and 1,2-dibromoethane (1.17 mL, 15.5 mmol) in MeCN (4 mL) was added K_2CO_3 (321 mg, 2.33 mmol). The mixture was stirred at 65 °C for 12 h. After cooling to room temperature, the mixture was diluted with H_2O (30 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (Biotage 4 g cartridge, 0–72% EtOAc/Petroleum ether) to give 7-(2-bromoethoxy)-4-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-3H,4H-pyrido[2,3-b]pyrazin-3-one. MS = 354.2 / 356.1 $[M+H]^+$.

Step 2: 5-chloro-1'-[2-({3-oxo-4-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-3H,4H-pyrido[2,3-b]pyrazin-7-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 358)

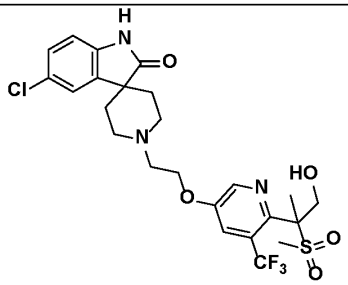
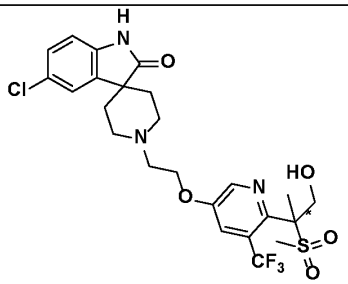


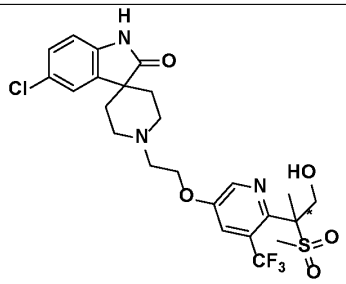
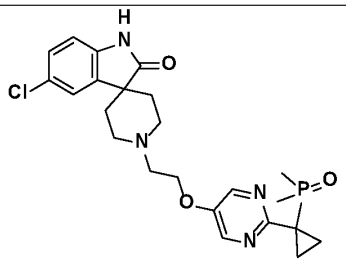
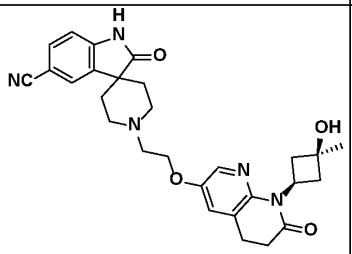
[1307] To a solution of 5-chloro-1'-[2-({3-oxo-4-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-3H,4H-pyrido[2,3-b]pyrazin-7-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (130 mg, 0.367 mmol) and 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 95.6 mg, 0.404 mmol, HCl salt) in MeCN (5 mL) was added $NaHCO_3$ (93.3 mg, 1.10 mmol). The mixture was stirred at 80 °C for 12 h. After cooling to room temperature, the mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters Xbridge OBD C_{18} column, 25–55% MeCN:10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-[2-({3-oxo-4-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-3H,4H-pyrido[2,3-b]pyrazin-7-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 358**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.54 – 10.45 (m, 1H), 8.44 (d, J = 2.8 Hz, 1H), 8.23 (s, 1H), 7.93 (d, J = 3.2 Hz, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.23 (dd, J = 8.4, 2.0 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 5.21 – 5.11 (m, 1H), 5.02 (s, 1H), 4.34 – 4.29 (m, 2H), 3.02 – 2.96 (m, 2H), 2.95 – 2.91 (m, 2H), 2.91 – 2.88 (m, 2H), 2.74 – 2.68 (m, 2H), 2.44 – 2.40 (m, 2H), 1.81 – 1.75 (m, 2H), 1.74 – 1.67 (m, 2H), 1.33 (s, 3H). MS = 510.1 $[M+H]^+$.

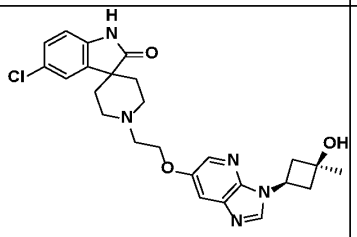
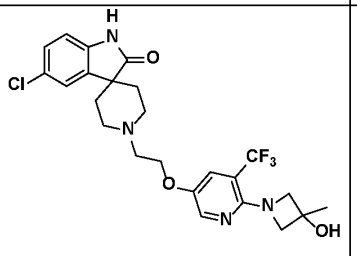
[1308] The following compounds in **Table 38.9** were prepared according to procedures analogous to those described for **Compound 358** using the appropriate starting materials or common intermediates.

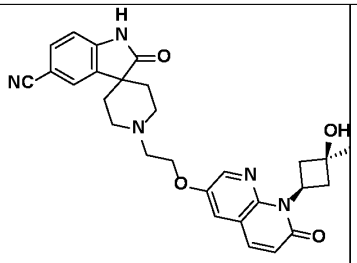
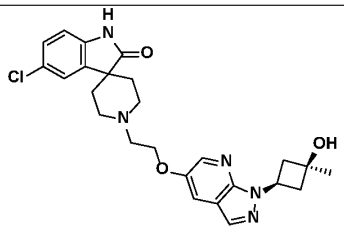
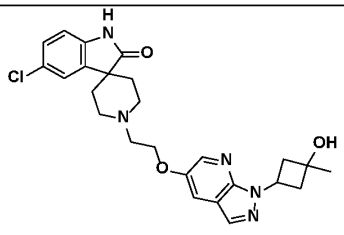
Table 38.9

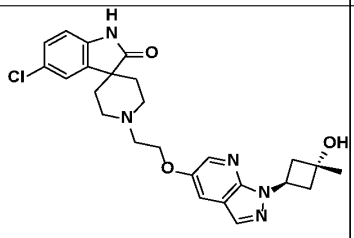
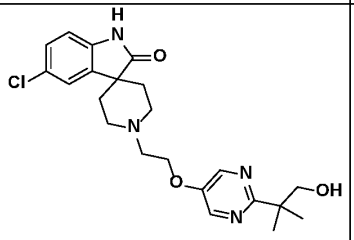
No.	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Inter-mediates Used	Chiral separat	Chiral elution order

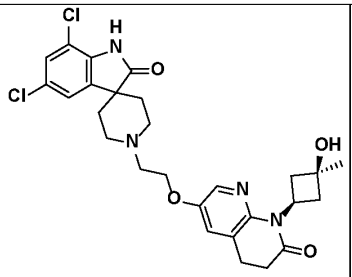
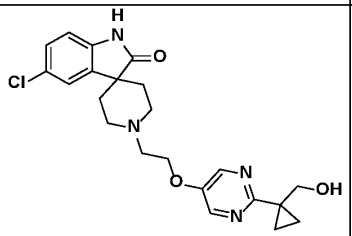
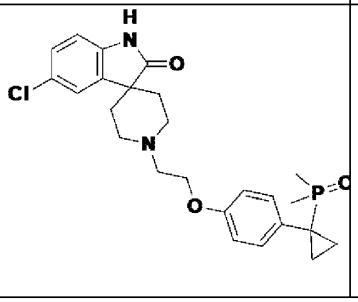
					ion column	
401		5-chloro-1'-(2-{[6-(1-hydroxy-2-methanesulfonylpropan-2-yl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 562.1 Found 562.0	**A-95 and B-4**	n/a	n/a
402		5-chloro-1'-[2-({6-[(2*S* or 2*R*)-1-hydroxy-2-methanesulfonylpropan-2-yl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 562.1 Found 561.9	**A-95 and B-4**	Daicel Chiralpak AD-3	1st

403		5-chloro-1'-[2-({6-[(2*R* or 2*S*)-1-hydroxy-2-methanesulfonylpropan-2-yl]-5-(trifluoromethyl)pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 562.1 Found 562.0	**A-95 and B-4**	Daicel Chiralpak AD-3	2nd
344		5-chloro-1'-[2-({2-[1-(dimethylphosphoryl)cyclopropyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 475.2 Found 475.2	**A-96 and B-4**	n/a	n/a
404		2-oxo-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-	Calc'd 502.2 Found 502.2	**A-89 and B-9**	n/a	n/a

		yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile				
367		5-chloro-1'-[2-({3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-3H-imidazo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 482.2 Found 482.2	**A-98 and B-4**	n/a	n/a
405		5-chloro-1'-(2-{[6-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 511.2 Found 511.2	**A-99 and B-4**	n/a	n/a

406		2-oxo-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 500.2 Found 500.3	**Example 68, Step 4 and B-9**	n/a	n/a
357		5-chloro-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-pyrazolo[3,4-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 482.2 Found 482.3	**A-116 and B-4**	Daicel Chiralpak AD	2nd
407		5-chloro-1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-1H-pyrazolo[3,4-b]pyridin-5-yl]oxy}ethyl)-1,2-	Calc'd 482.2 Found 482.1	**A-116 and B-4**	n/a	n/a

		dihydrospiro[indole-3,4'-piperidin]-2-one				
408		5-chloro-1'-[2-({1-[(*trans*)-3-hydroxy-3-methylcyclobutyl]-1H-pyrazolo[3,4-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 482.2 Found 482.1	**A-116 and B-4**	Daicel Chiralpak AD	1st
334		5-chloro-1'-(2-{[2-(1-hydroxy-2-methylpropan-2-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 431.2 Found 431.2	**A-100 and B-4**	n/a	n/a

409		5,7-dichloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 545.2 Found 545.2	**General Procedure for Intermediate A-89, Step 3 and Example3, Step 2**	n/a	n/a
333*		5-chloro-1'-[2-({2-[1-(hydroxymethyl)cyclopropyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 429.2 Found 429.1	**A-101 and B-4**	n/a	n/a
343		5-chloro-1'-(2-{4-[1-(dimethylphosphoryl)cyclopropyl]phenoxy}ethyl)-1,2-	Calc'd 473.2 Found 473.3	**A-102 and B-4**	n/a	n/a

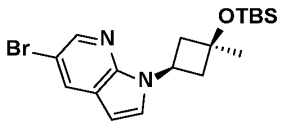
		dihydrospiro[indole-3,4'-piperidin]-2-one				

* Prepared according to procedures analogous to Step 2 in procedure for synthesis of **Compound 358**

Example 78

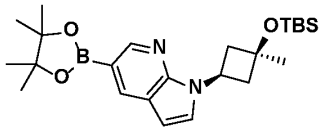
5-chloro-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 349)

Step 1: [5-bromo-1-[(*cis*)-3-[(tert-butyldimethylsilyl)oxy]-3-methylcyclobutyl]-1H-pyrrolo[2,3-b]pyridine



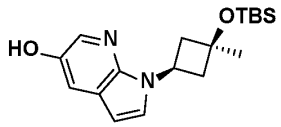
[1309] To a mixture of 5-bromo-1H-pyrrolo[2,3-b]pyridine (5.00 g, 25.4 mmol) and *tert*-butyldimethyl[(*cis*)-3-bromo-1-methylcyclobutoxy]silane (10.6 g, 38.1 mmol) in DMF (80 mL) was added Cs_2CO_3 (20.7 g, 63.4 mmol). The mixture was stirred at 90 °C for 30 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (200 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 120 g cartridge, 0–10% EtOAc/Petroleum ether), and then further purified by reverse phase preparative HPLC (Phenomenex C_{18} column, 75–99% MeCN:10 mM NH_4HCO_3 in H_2O) to give *tert*-butyldimethyl[(*cis*)-3-bromo-1-methylcyclobutoxy]silane. MS = 395.0 / 397.0 $[M+H]^+$.

Step 2: 1-[(*cis*)-3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine



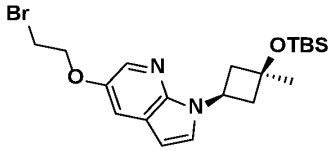
[1310] A mixture of bis(pinacolato)diboron (1.41 g, 5.55 mmol), *tert*-butyldimethyl[(*cis*)-3-bromo-1-methylcyclobutoxy]silane (1.83 g, 4.63 mmol), KOAc (908 mg, 9.26 mmol) and Pd(dppf)Cl_2 (169 mg, 231 μmol) in 1,4-dioxane (20 mL) was degassed and purged with N_2 (3x), and then the mixture was stirred at 80 °C for 15 h under N_2 atmosphere. After cooling to room temperature, the reaction mixture was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to give 1-[(*cis*)-3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine, which was taken to the next step without further purification. MS = 443.2 $[M+H]^+$..

Step 3: 1-[(*cis*)-3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl]-1H-pyrrolo[2,3-b]pyridin-5-ol



[1311] To a 0 °C solution of 1-[(*cis*)-3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine (2.05 g, 4.63 mmol) in acetone (20 mL) and H_2O (20 mL) was added Oxone (1.42 g, 2.32 mmol). The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3 x 40 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 40 g cartridge, 0–50% EtOAc/Petroleum ether) to give 1-[(*cis*)-3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl]-1H-pyrrolo[2,3-b]pyridin-5-ol. MS = 333.1 $[M+H]^+$.

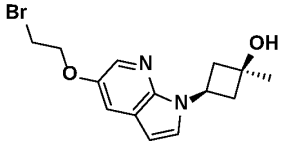
Step 4: 5-(2-bromoethoxy)-1-[(*cis*)-3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl]-1H-pyrrolo[2,3-b]pyridine



[1312] To a mixture of 1,2-dibromoethane (7.68 g, 40.9 mmol) and 1-[(*cis*)-3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl]-1H-pyrrolo[2,3-b]pyridin-5-ol (340 mg, 1.02 mmol) in MeCN (5 mL) was added K_2CO_3 (707 mg, 5.11 mmol). The mixture was stirred at 85 °C for 63 h.

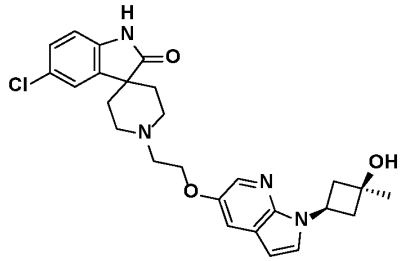
After cooling to room temperature, the reaction mixture was diluted with H_2O (10 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 20 g cartridge, 0–100% EtOAc/Petroleum ether) to give 5-(2-bromoethoxy)-1-[(*cis*)-3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl]-1H-pyrrolo[2,3-b]pyridine. MS = 439.0 / 441.0 $[M+H]^+$.

Step 5: (*cis*)-3-[5-(2-bromoethoxy)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1-methylcyclobutan-1-ol



[1313] A solution of 5-(2-bromoethoxy)-1-[(*cis*)-3-[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclobutyl]-1H-pyrrolo[2,3-b]pyridine (485 mg, 1.10 mmol) in 4.0 M HCl in EtOAc (5.0 mL, 20 mmol) was stirred at room temperature for 2 h. The reaction mixture was filtered and the filter cake was washed with Petroleum ether (3 x 1 mL) and dried under reduced pressure to give (*cis*)-3-[5-(2-bromoethoxy)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1-methylcyclobutan-1-ol (HCl salt), which was taken to the next step without further purification. MS = 325.0 / 327.0 $[M+H]^+$.

Step 6: 5-chloro-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 349)

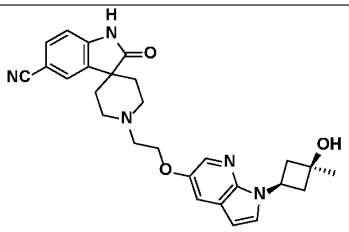


[1314] To a mixture of (*cis*)-3-[5-(2-bromoethoxy)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1-methylcyclobutan-1-ol (100 mg, 277 µmol, HCl salt) and 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 98.2 mg, 359 µmol, HCl salt) in MeCN (2 mL) was added $NaHCO_3$ (116 mg, 1.38 mmol). The mixture was stirred at 80 °C for 15 h. After cooling to room temperature, the reaction mixture was concentrated. The residue was purified by reverse phase preparative HPLC (Waters Xbridge BEH C_{18} column, 30–60% MeCN:10 mM NH_4HCO_3 in H_2O) to

give 5-chloro-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 349**). MS = 481.0 $[M+H]^+$.

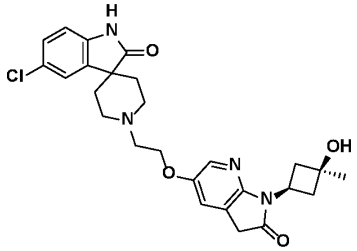
[1315] The following compounds in **Table 38.10** were prepared according to procedures analogous to those described for **Compound 349** using the appropriate starting materials or common intermediates.

Table 38.10

No.	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Intermediate Used
410		2-oxo-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 472.2 Found 472.2	**B-9**

Example 79

5-chloro-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 347)

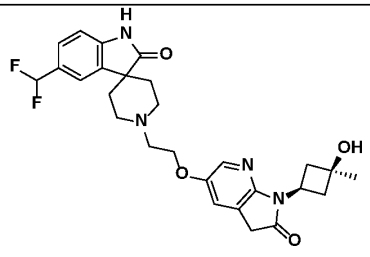


[1316] To a round-bottom flask equipped with a magnetic stir bar were added 5-chloro-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-

dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 349**, 64.0 mg, 133 µmol), *t*-BuOH (2 mL), H_2O (0.2 mL) and then Py•Br_3 (128 mg, 399 µmol). The mixture was stirred at room temperature for 3 h. The mixture was diluted with H_2O (3 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in AcOH (1 mL) and then Zinc (8.70 mg, 133 µmol) was added. The mixture was stirred at room temperature for 4 h. The reaction mixture was cooled to 0 °C and quenched with H_2O (10 mL), and then adjusted to pH = 7 by addition of saturated aqueous $NaHCO_3$ solution. The mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase preparative HPLC (Waters Xbridge Prep OBD C_{18} column, 20–55% MeCN:10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 347**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 7.89 (d, J = 2.8 Hz, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.42 (d, J = 2.8 Hz, 1H), 7.24 (dd, J = 8.0, 2.0 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 5.12 (s, 1H), 4.39 – 4.37 (m, 1H), 4.16 (t, J = 5.6 Hz, 2H), 3.56 (s, 2H), 3.01 – 2.91 (m, 2H), 2.85 – 2.84 (m, 2H), 2.82 – 2.83 (m, 2H), 2.68 – 2.69 (m, 2H), 2.23 – 2.20 (m, 2H), 1.78 – 1.72 (m, 4H), 1.30 (s, 3H). MS = 497.2 $[M+H]^+$.

[1317] The following compounds in **Table 38.11** were prepared according to procedures analogous to those described for **Compound 347** using the appropriate starting materials or common intermediates.

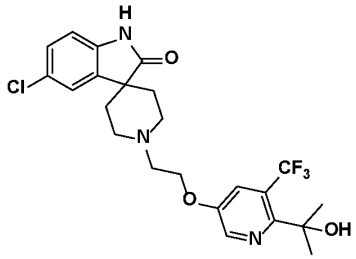
Table 38.11

#	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Inter-mediate used
348		5-(difluoromethyl)-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H-pyrrolo[2,3-b]pyridin-5-yl}oxy)ethyl]-1,2-	Calc'd 513.2 Found 513.2	**B-1**

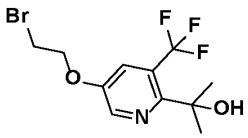
		dihydrospiro[indole-3,4'-piperidin]-2-one		

Example 80

5-chloro-1'-(2-{[6-(2-hydroxypropan-2-yl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 371)

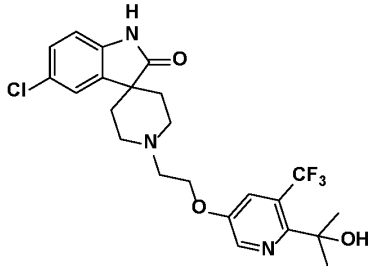


Step 1: 2-[5-(2-bromoethoxy)-3-(trifluoromethyl)pyridin-2-yl]propan-2-ol



[1318] To a solution of 1-[5-(2-bromoethoxy)-3-(trifluoromethyl)pyridin-2-yl]ethan-1-one (**Example 71, Step 5**, 100 mg, 320 μmol) in THF (2 mL) at 0 °C was added 3.0 M MeMgBr in THF (160 μL, 480 μmmol). The mixture was stirred at 0 °C for 2 h, then was quenched by addition of H_2O (1 mL) and extracted with EtOAc (3 x 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 2-[5-(2-bromoethoxy)-3-(trifluoromethyl)pyridin-2-yl]propan-2-ol, which was taken to the next step without further purification. MS = 328.0 / 330.0 $[M+H]^+$.

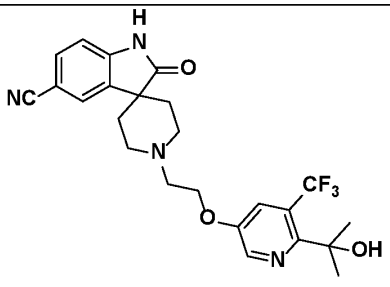
Step 2: 5-chloro-1'-(2-{[6-(2-hydroxypropan-2-yl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one



[1319] To a solution of 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 93.7 mg, 305 µmol, HCl salt) in MeCN (5 mL) was added $NaHCO_3$ (154 mg, 1.83 mmol) and 2-[5-(2-bromoethoxy)-3-(trifluoromethyl)pyridin-2-yl]propan-2-ol (100 mg, 305 µmol). The mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the mixture was concentrated in vacuo. The residue was purified by reverse phase preparative HPLC (Phenomenex Luna C_{18} column, 10–50% MeCN:10 mM TFA in H_2O) to give 5-chloro-1'-(2-{[6-(2-hydroxypropan-2-yl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 371**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.66 – 10.20 (m, 1H), 8.49 (d, J = 2.4 Hz, 1H), 7.69 (d, J = 2.4 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.30 – 7.18 (m, 1H), 6.85 (d, J = 8.4 Hz, 1H), 5.15 (br d, J = 1.2 Hz, 1H), 4.31 (t, J = 5.6 Hz, 2H), 3.05 – 2.82 (m, 4H), 2.77 – 2.64 (m, 2H), 1.86 – 1.62 (m, 4H), 1.51 (s, 6H). MS = 484.3 $[M+H]^+$.

[1320] The following compounds in **Table 38.12** were prepared according to procedures analogous to those described for **Compound 371** using the appropriate starting materials or common intermediates.

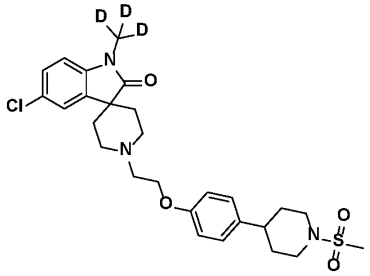
Table 38.12

#	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Intermediate used
411		1'-(2-{[6-(2-hydroxypropan-2-yl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-	Calc'd 475.2 Found 475.1	**B-9**

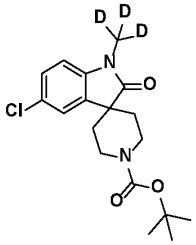
		3,4'-piperidine]-5-carbonitrile		

Example 81

5-chloro-1'-{2-[4-(1-methanesulfonylpiperidin-4-yl)phenoxy]ethyl}-1-($^2H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 412)

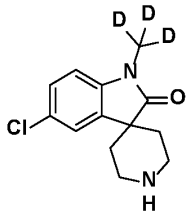


Step 1: *tert*-butyl 5-chloro-1-($^2H_3$)methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate



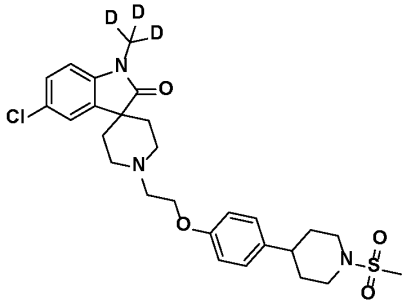
[1321] To a three-neck round-bottom flask equipped with a thermometer under N_2 atmosphere were added *tert*-butyl 5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (**Intermediate B-3**, 8.67 g, 25.8 mmol), CD_3I (5.60 g, 38.6 mmol) and THF (100 mL). The mixture was cooled to 0 °C and sodium hydride (3.09 g, 60% in mineral oil, 77.3 mmol) was added in portions. The mixture was stirred at 0 °C for 3 h under N_2 atmosphere. The reaction mixture was maintained at 0–5 °C and quenched by addition of saturated aqueous NH_4Cl (100 mL), and then extracted with EtOAc (3 x 150 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 120 g cartridge, 0–40% EtOAc/Petroleum ether) to give *tert*-butyl 5-chloro-1-($^2H_3$)methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate. MS = 297.9 $[M–C_4H_8+H]^+$.

Step 2: 5-chloro-1-(trideuteriomethyl)spiro[indoline-3,4'-piperidine]-2-one



[1322] To a mixture of *tert*-butyl 5-chloro-1-($^2H_3$)methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-1'-carboxylate (8.60 g, 24.3 mmol) in EtOAc (10 mL) was added 4.0 M HCl in EtOAc (90 mL, 360 mmol). The mixture was stirred at room temperature for 2 h, then concentrated in vacuo. The residue was triturated with MTBE (45 mL) at room temperature for 1 h, and solids were collected by filtration. The filter cake was dried in vacuo to give 5-chloro-1-($^2H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (HCl salt), which was taken to the next step without further purification. MS = 254.2 $[M+H]^+$.

Step 3: 5-chloro-1'-{2-[4-(1-methanesulfonylpiperidin-4-yl)phenoxy]ethyl}-1-($^2H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

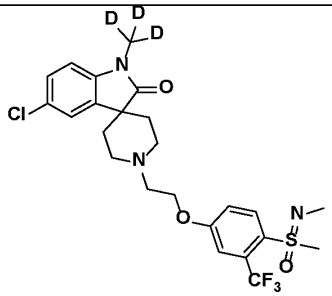
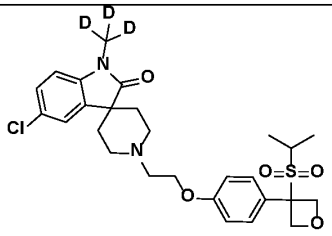
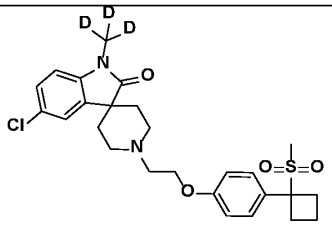


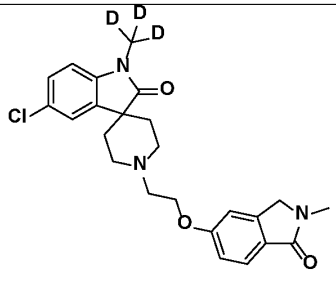
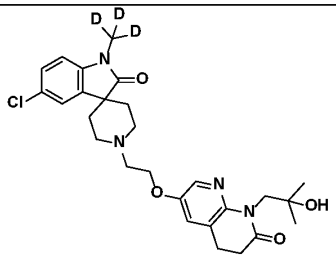
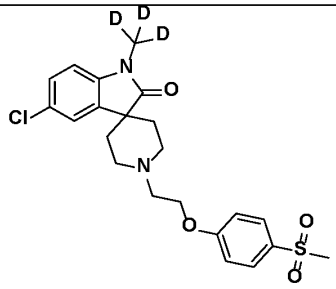
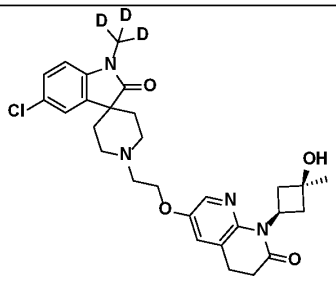
[1323] To a solution of 5-chloro-1-($^2H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (88.1 mg, 304 μmol, HCl salt) in MeCN (3 mL) was added $NaHCO_3$ (92.8 mg, 1.10 mmol) and 4-[4-(2-bromoethoxy)phenyl]-1-methanesulfonylpiperidine (**Intermediate A-104**, 100 mg, 276 μmol). The mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was filtered to remove $NaHCO_3$. The filtrate was purified by reverse phase preparative HPLC (Waters Xbridge Prep OBD C_{18} column, 35–65% MeCN:10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-{2-[4-(1-methanesulfonylpiperidin-4-yl)phenoxy]ethyl}-1-($^2H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 412**). ^1H NMR (400 MHz, DMSO-d_6): δ

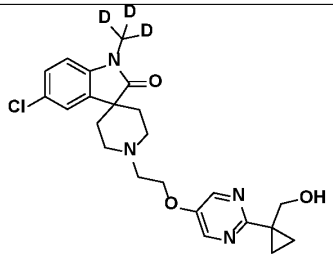
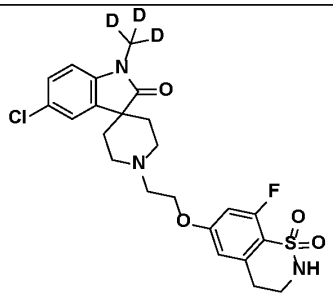
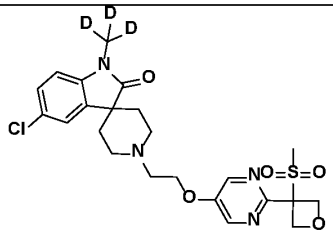
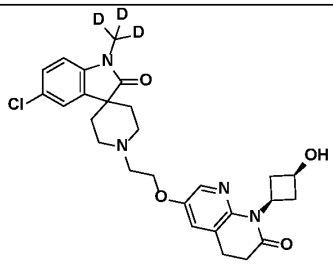
7.56 (d, J = 2.0 Hz, 1H), 7.35 (dd, J = 8.0, 2.0 Hz, 1H), 7.18 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 8.4 Hz, 2H), 4.11 (t, J = 5.6 Hz, 2H), 3.66 (d, J = 12.0 Hz, 2H), 2.97 – 2.90 (m, 2H), 2.89 (s, 3H), 2.84 (t, J = 5.6 Hz, 2H), 2.82 – 2.75 (m, 2H), 2.74 – 2.67 (m, 2H), 2.60 – 2.54 (m, 1H), 1.86 – 1.70 (m, 6H), 1.68 – 1.57 (m, 2H). MS = 535.3 $[M+H]^+$.

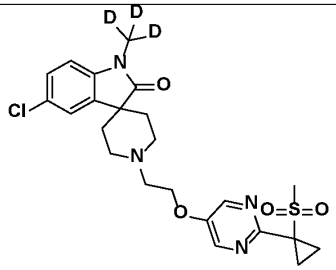
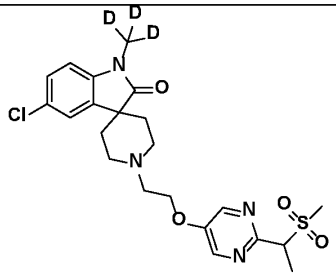
[1324] The following compounds in **Table 38.13** were prepared according to procedures analogous to those described for **Compound 412** using the appropriate starting materials or common intermediates.

Table 38.13

#	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Intermediate used
413		5-chloro-1-($^2H_3$)methyl-1'-(2-{4-[methyl(methylimino)oxo-λ^6-sulfanyl]-3-(trifluoromethyl)phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 533.2 Found 533.3	**A-103**
414		5-chloro-1-($^2H_3$)methyl-1'-(2-{4-[3-(propane-2-sulfonyl)oxetan-3-yl]phenoxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 536.2 Found 536.2	**A-107**
415		5-chloro-1'-{2-[4-(1-methanesulfonylcyclobutyl)phenoxy]ethyl}-1-($^2H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 506.2 Found 506.3	**A-40**

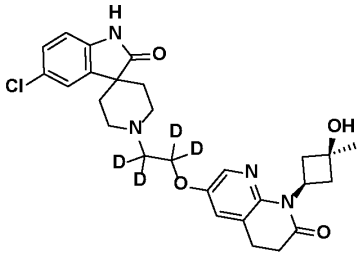
416		5-chloro-1-($^2H_3$)methyl-1'-{2-[(2-methyl-1-oxo-2,3-dihydro-1H-isoindol-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 443.2 Found 443.2	**A-53**
417		5-chloro-1'-(2-{[8-(2-hydroxy-2-methylpropyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1-($^2H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 516.2 Found 516.3	**A-106**
418		5-chloro-1'-[2-(4-methanesulfonylphenoxy)ethyl]-1-($^2H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 452.1 Found 452.2	**A-3**
419		5-chloro-1-($^2H_3$)methyl-1'-[2-({7-oxo-8-[(1r,3s)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 528.2 Found 528.2	**A-89**

420		5-chloro-1'-[2-({2-[1-(hydroxymethyl)cyclopropyl]pyrimidin-5-yl}oxy)ethyl]-1-($^2H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 446.2 Found 446.1	**A-101**
421		6-{2-[5-chloro-1-($^2H_3$)methyl-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl]ethoxy}-8-fluoro-3,4-dihydro-2H-1λ^6,2-benzothiazine-1,1-dione	Calc'd 497.1 Found 497.2	
422		5-chloro-1'-(2-{[2-(3-methanesulfonyloxetan-3-yl)pyrimidin-5-yl]oxy}ethyl)-1-($^2H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 510.2 Found 510.3	**A-88**
423		5-chloro-1-($^2H_3$)methyl-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxycyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 514.2 Found 514.1	**A-79**

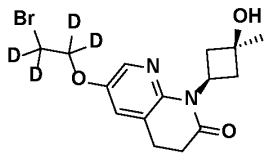
424		5-chloro-1'-(2-{[2-(1-methanesulfonylcyclopropyl) pyrimidin-5-yl]oxy}ethyl)-1-($^2H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 494.2 Found 494.1	**A-76**
425		5-chloro-1'-(2-{[2-(1-methanesulfonylethyl)pyrimidin-5-yl]oxy}ethyl)-1-($^2H_3$)methyl-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 482.2 Found 482.1	**A-75**

Example 82

5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)(1,1,2,2-$^2H_4$)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 426)



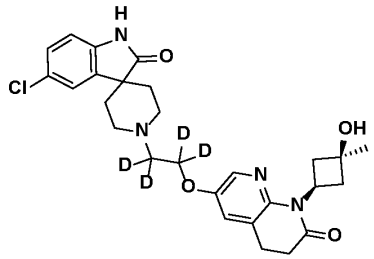
Step 1: 6-[2-bromo(1,1,2,2-$^2H_4$)ethoxy]-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



[1325] A mixture of 6-hydroxy-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-3,4-dihydro-1,8-naphthyridin-2-one (General Procedure for Intermediate A-89, Step 3, 100 mg, 0.403 mmol)

and Cs_2CO_3 (262 mg, 0.806 mmol) in dibromo($^2H_4$)ethane (1.55 g, 8.05 mmol) and DMF (0.5 mL) was stirred at 90 °C for 3 h. The mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by flash silica gel chromatography (Biotage 10 g cartridge, 0–100% EtOAc/hexane) to give 6-[2-bromo(1,1,2,2-$^2H_4$)ethoxy]-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-3,4-dihydro-1,8-naphthyridin-2-one. MS = 359.2 / 361.2 $[M+H]^+$.

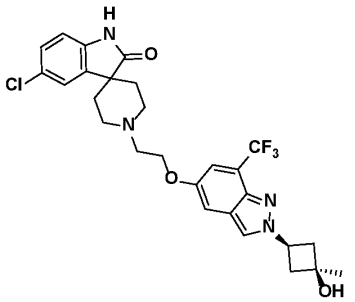
Step 2: 5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)(1,1,2,2-$^2H_4$)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one



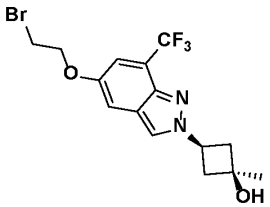
[1326] A mixture of 6-[2-bromo(1,1,2,2-$^2H_4$)ethoxy]-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-3,4-dihydro-1,8-naphthyridin-2-one (60.0 mg, 0.167 mmol), 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 50.2 mg, 0.184 mmol), K_2CO_3 (57.7 mg, 0.418 mmol) and KI (14 mg, 0.084 mmol) in DMF (1 mL) was stirred at 60 °C for 3 h. The mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase silica gel chromatography (Biotage 60 g C_{18} cartridge, 5–50% MeCN/H_2O with 0.1% NH_4OH) to give 5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5,6-dihydro-1,8-naphthyridin-3-yl}oxy)(1,1,2,2-$^2H_4$)ethyl]-1H-spiro[indole-3,4'-piperidin]-2-one (**Compound 426**). ^1H NMR (500 MHz, DMSO-d_6): δ 10.54 (s, 1H), 7.95 (d, J = 2.9 Hz, 1H), 7.52 (s, 1H), 7.40 (d, J = 2.9 Hz, 1H), 7.25 (dd, J = 8.3, 2.1 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 4.82 (s, 1H), 4.24 (pent, J = 8.3 Hz, 1H), 3.20 – 2.67 (m, 4H), 2.54 – 2.50 (m, 4H), 2.48 – 2.40 (m, 2H), 2.38 – 2.30 (m, 2H), 2.00 – 1.61 (m, 4H), 1.25 (s, 3H). MS = 515.2 $[M+H]^+$.

Example 83

5-chloro-1'-[2-({2-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2H-indazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 427)

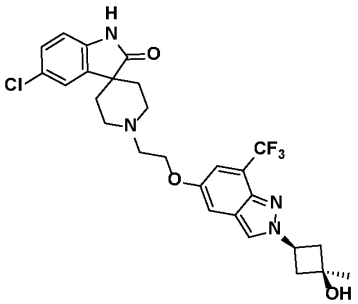


Step 1: (*cis*)-3-[5-(2-bromoethoxy)-7-(trifluoromethyl)-2H-indazol-2-yl]-1-methylcyclobutan-1-ol



[1327] A mixture of 2-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2H-indazol-5-ol (**Intermediate A-108**, 365 mg, 1.27 mmol) and Cs_2CO_3 (831 mg, 2.55 mmol) in 1,2-dibromoethane (3.3 mL, 38.2 mmol) and DMF (0.5 mL) was stirred at 90 °C for 19 h. The mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by flash silica gel chromatography (Biotage 25 g cartridge, 0–100% EtOAc/hexane) to give (*cis*)-3-[5-(2-bromoethoxy)-7-(trifluoromethyl)-2H-indazol-2-yl]-1-methylcyclobutan-1-ol. MS = 393.1 / 395.1 $[M+H]^+$.

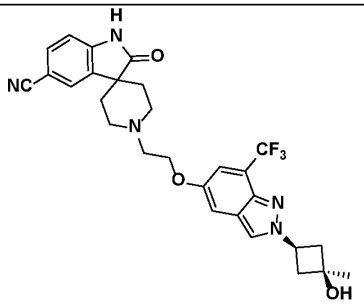
Step 2: 5-chloro-1'-[2-({2-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2H-indazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 427)



[1328] A mixture of (*cis*)-3-[5-(2-bromoethoxy)-7-(trifluoromethyl)indazol-2-yl]-1-methylcyclobutan-1-ol (85 mg, 0.216 mmol), 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 65 mg, 0.238 mmol, HCl salt), K_2CO_3 (75 mg, 0.54 mmol) and KI (18 mg, 0.108 mmol) in DMF (1 mL) was stirred at 60 °C for 4 h. The mixture was cooled to room temperature, filtered, washed with EtOAc (3 x 20 mL). The filtrate was concentrated under reduced pressure. The crude residue was purified by reverse phase preparative HPLC (Phenomenex Kinetex C_{18} column, 5-40% MeCN in H_2O with 0.1% formic acid) to give 5-chloro-1'-[2-({2-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2H-indazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 427**). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.47 (s, 1H), 8.43 (s, 1H), 7.45 (s, 1H), 7.38 (d, J = 2.3 Hz, 1H), 7.27 (s, 1H), 7.18 (dd, J = 8.3, 2.1 Hz, 1H), 6.79 (d, J = 8.2 Hz, 1H), 5.27 (s, 1H), 4.80 (pent, J = 8.3 Hz, 1H), 4.19 – 4.16 (m, 2H), 3.13 – 2.68 (m, 6H), 2.61 – 2.48 (m, 4H), 1.90 – 1.61 (m, 4H), 1.30 (s, 3H). MS = 549.1 $[M+H]^+$.

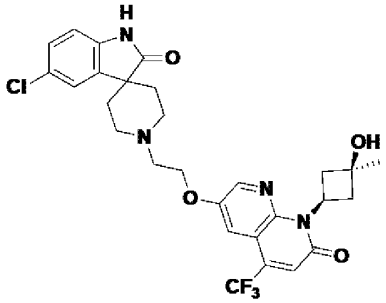
[1329] The following compound in **Table 38.14** was prepared according to the procedures analogous to those described for **Compound 427** using the appropriate starting materials.

Table 38.14

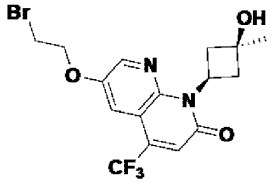
No.	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Inter-mediate used
428		2-oxo-1'-[2-({2-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2H-indazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 540.2 Found 540.2	**A-108** and **B-9**

Example 84

5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5-(trifluoromethyl)-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 341)

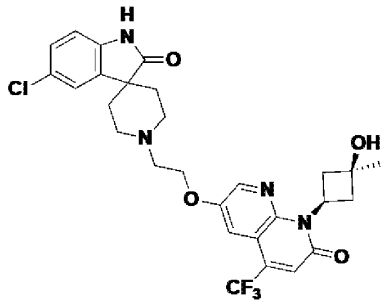


Step 1: 6-(2-bromoethoxy)-1-((*cis*)-3-hydroxy-3-methylcyclobutyl)-4-(trifluoromethyl)-1,8-naphthyridin-2(1H)-one



[1330] To a mixture of 6-hydroxy-1-((*cis*)-3-hydroxy-3-methylcyclobutyl)-4-(trifluoromethyl)-1,8-naphthyridin-2(1H)-one (**Intermediate A-109**, 400 mg, 1.27 mmol) and 1,2-dibromoethane (2.88 mL, 38.2 mmol) in MeCN (5 mL) was added K_2CO_3 (704 mg, 5.09 mmol). The mixture was stirred at 65 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–15% EtOAc/Petroleum ether) to give 6-(2-bromoethoxy)-1-((*cis*)-3-hydroxy-3-methylcyclobutyl)-4-(trifluoromethyl)-1,8-naphthyridin-2(1H)-one. MS = 420.9 / 422.8 $[M+H]^+$.

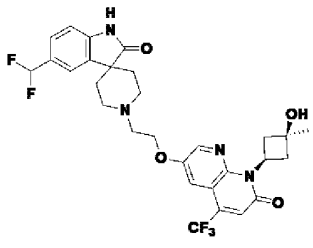
Step 2: 5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5-(trifluoromethyl)-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

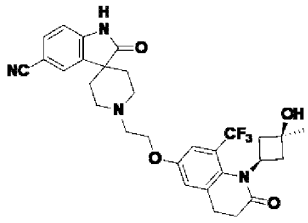
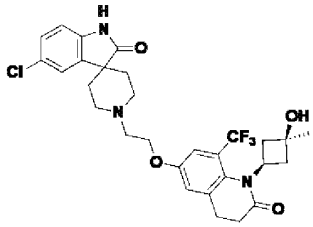
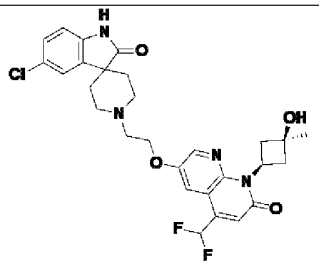


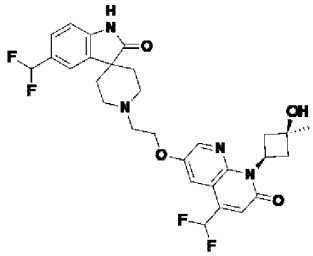
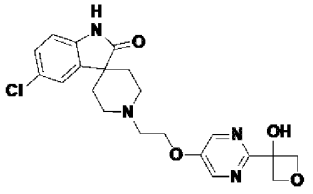
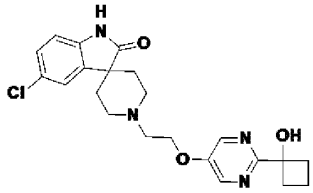
[1331] To a mixture of 6-(2-bromoethoxy)-1-((*cis*)-3-hydroxy-3-methylcyclobutyl)-4-(trifluoromethyl)-1,8-naphthyridin-2(1H)-one (120 mg, 285 µmol) and 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 77.82 mg, 285 µmol, HCl salt) in MeCN (3 mL) was added $NaHCO_3$ (120 mg, 1.42 mmol). The mixture was stirred at 65 °C for 16 h. After cooling to room temperature, the reaction was diluted with H_2O (10 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Waters Xbridge OBD C_{18} column, 30–60% MeCN:10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5-(trifluoromethyl)-7,8-dihydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 341**). ^{1}H NMR (400 MHz, MeCN-d_3): δ 8.48 (d, J = 2.8 Hz, 1H), 8.39 (br s, 1H), 7.66 – 7.59 (m, 1H), 7.43 (d, J = 2.0 Hz, 1H), 7.20 (dd, J = 8.4, 2.0 Hz, 1H), 7.08 (s, 1H), 6.87 (d, J = 8.4 Hz, 1H), 5.77 – 5.65 (m, 1H), 4.28 (t, J = 5.6 Hz, 2H), 3.87 (s, 1H), 3.08 – 2.86 (m, 6H), 2.80 – 2.67 (m, 2H), 2.61 – 2.49 (m, 2H), 1.91 – 1.81 (m, 2H), 1.79 – 1.69 (m, 2H), 1.37 (s, 3H). MS = 577.3 $[M+H]^+$.

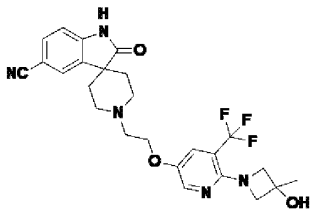
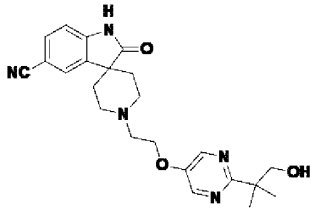
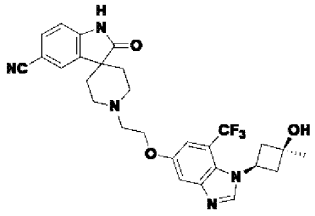
[1332] The following compounds in **Table 38.15** were prepared according to procedures analogous to those described for **Compound 341** using the appropriate starting materials or common intermediates.

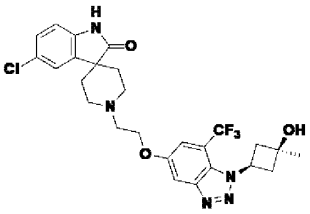
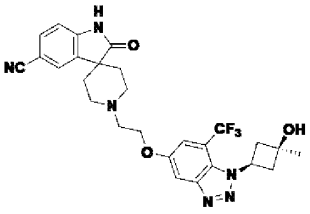
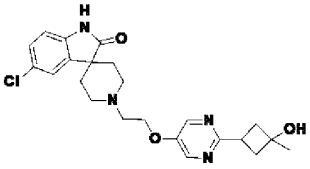
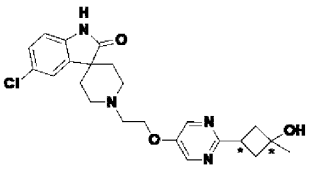
Table 38.15

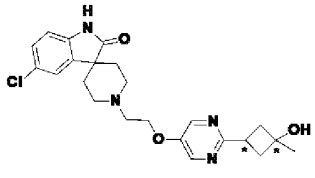
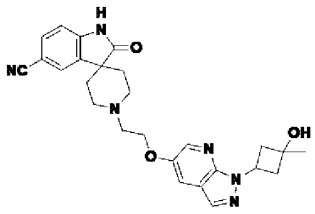
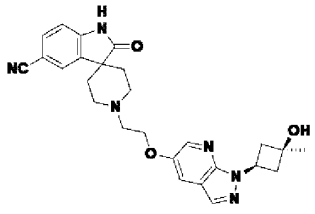
#	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Inter-mediates Used	Chiral separation column	Chiral elution order
342		5-(difluoromethyl)-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5-(trifluoromethyl)-7,8-dihydro-1,8-	Calc'd 593.2 Found 593.3	**A-109** and **B-1**	n/a	n/a

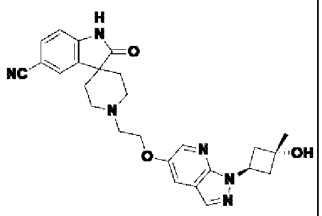
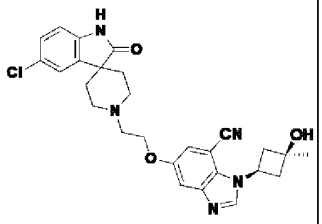
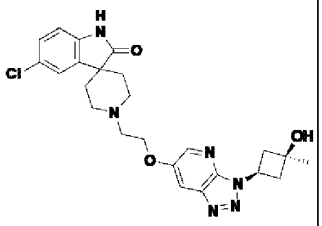
		naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one				
354		2-oxo-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 569.2 Found 569.2	**A-110** and **B-9**	n/a	n/a
353		5-chloro-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 578.2 Found 578.2	**A-110** and **B-4**	n/a	n/a
339		5-chloro-1'-(2-{[5-(difluoromethyl)-7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-	Calc'd 559.2 Found 559.4	**A-111** and **B-4**	n/a	n/a

		7,8-dihydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one				
340		5-(difluoromethyl)-1'-(2-{[5-(difluoromethyl)-7-oxo-8-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7,8-dihydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 575.2 Found 575.4	**A-111** and **B-1**	n/a	n/a
429		5-chloro-1'-(2-{[2-(3-hydroxyoxetan-3-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 431.1 Found 431.2	**A-112** and **B-4**	n/a	n/a
430		5-chloro-1'-(2-{[2-(1-hydroxycyclobutyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 429.1 Found 429.1	**A-113** and **B-4**	n/a	n/a

431		1'-(2-{[6-(3-hydroxy-3-methylazetidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 502.2 Found 502.3	**A-99** and **B-9**	n/a	n/a
432		1'-(2-{[2-(1-hydroxy-2-methylpropan-2-yl)pyrimidin-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 422.2 Found 422.2	**A-100** and **B-9**	n/a	n/a
433		1'-(2-((1-((*cis*)-3-hydroxy-3-methylcyclobutyl)-7-(trifluoromethyl)-1H-benzo[d]imidazol-5-yl)oxy)ethyl)-2-oxospiro[indoline-3,4'-piperidine]-5-carbonitrile	Calc'd 540.2 Found 540.1	**A-92** and **B-9**	n/a	n/a

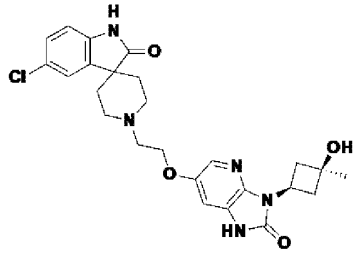
434		5-chloro-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,2,3-benzotriazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 550.2 Found 550.0	**A-114 and B-4**	n/a	n/a
435		2-oxo-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,2,3-benzotriazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 541.2 Found 541.0	**A-114** and **B-9**	n/a	n/a
373		5-chloro-1'-(2-{[2-(3-hydroxy-3-methylcyclobutyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 443.2 Found 443.0	**A-115** and **B-4**	n/a	n/a
393		5-chloro-1'-[2-({2-[(*cis*) or (*trans*)-3-hydroxy-3-methylcyclobutyl]pyrimidin-5-	Calc'd 443.2 Found 443.0	**A-115** and **B-4**	Daicel Chiralpak AD-3	1st

		yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one				
392		5-chloro-1'-[2-({2-[(*trans*) or (*cis*)-3-hydroxy-3-methylcyclobutyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 443.2 Found 443.0	**A-115** and **B-4**	Daicel Chiralpak AD-3	2nd
436		1'-(2-{[1-(3-hydroxy-3-methylcyclobutyl)-1H-pyrazolo[3,4-b]pyridin-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 473.2 Found 473.1	**A-116** & **B-9**	n/a	n/a
437		2-oxo-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-pyrazolo[3,4-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 473.2 Found 473.1	**A-116** & **B-9**	Daicel Chiralpak OJ-3	1st

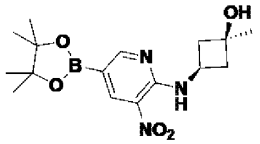
438		2-oxo-1'-[2-({1-[(*trans*)-3-hydroxy-3-methylcyclobutyl]-1H-pyrazolo[3,4-b]pyridin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 473.2 Found 473.1	**A-116** & **B-9**	Daicel Chiralpak OJ-3	2nd
439		5-(2-{5-chloro-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidin]-1'-yl}ethoxy)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazole-7-carbonitrile	Calc'd 506.2 Found 506.2	**A-117** & **B-4**	n/a	n/a
440		5-chloro-1'-[2-({3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-3H-[1,2,3]triazolo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 483.2 Found 483.2	**A-118** & **B-4**	n/a	n/a

Example 85

5-chloro-1'-[2-({2-oxo-3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H-imidazo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 374)

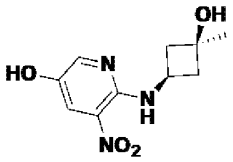


Step 1: (*cis*)-1-methyl-3-((3-nitro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)amino)cyclobutan-1-ol



[1333] A mixture of (*cis*)-3-((5-bromo-3-nitropyridin-2-yl)amino)-1-methylcyclobutan-1-ol (General procedure for **Intermediate A-92**, Step 2, 1.00 g, 3.31 mmol), bis(pinacolato)diboron (1.68 g, 6.62 mmol), KOAc (650 mg, 6.62 mmol) and Pd(dppf)Cl_2 (121 mg, 165 μmol) in 1,4-dioxane (15 mL) was degassed and purged with N_2 for 10 min, and then stirred at 85 °C for 16 h under N_2 atmosphere. After cooling to room temperature, the mixture was filtered, and the filtrate was concentrated in vacuo to give (*cis*)-1-methyl-3-((3-nitro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)amino)cyclobutan-1-ol, which was used in the subsequent step without further purification. MS= 267.9 $[M-C_6H_{10}+H]^+$.

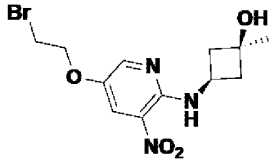
Step 2: 6-(((*cis*)-3-hydroxy-3-methylcyclobutyl)amino)-5-nitropyridin-3-ol



[1334] To a solution of 1(*cis*)-1-methyl-3-((3-nitro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)amino)cyclobutan-1-ol (1.00 g, 2.86 mmol) in THF (10 mL) and H_2O (10 mL) was added Oxone (1.76 g, 2.86 mmol). The mixture was stirred at room temperature for 2 h, then was diluted with H_2O (30 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers

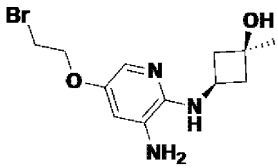
were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–85% EtOAc/Petroleum ether) to give 6-(((*cis*)-3-hydroxy-3-methylcyclobutyl)amino)-5-nitropyridin-3-ol. MS= 239.9 $[M+H]^+$.

Step 3: (*cis*)-3-((5-(2-bromoethoxy)-3-nitropyridin-2-yl)amino)-1-methylcyclobutan-1-ol



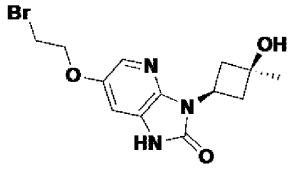
[1335] To a solution of 6-(((*cis*)-3-hydroxy-3-methylcyclobutyl)amino)-5-nitropyridin-3-ol (1.00 g, 4.18 mmol) in MeCN (20 mL) was added K_2CO_3 (2.31 g, 16.7 mmol) and 1,2-dibromoethane (6.31 mL, 83.6 mmol). The mixture was stirred at 65 °C for 12 h. After cooling to room temperature, the mixture was diluted with H_2O (10 mL) and extracted with DCM (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 20 g cartridge, 0–65% EtOAc/Petroleum ether) to give (*cis*)-3-((5-(2-bromoethoxy)-3-nitropyridin-2-yl)amino)-1-methylcyclobutan-1-ol. MS = 346.1 / 348.1 $[M+H]^+$.

Step 4: (*cis*)-3-((3-amino-5-(2-bromoethoxy)pyridin-2-yl)amino)-1-methylcyclobutan-1-ol



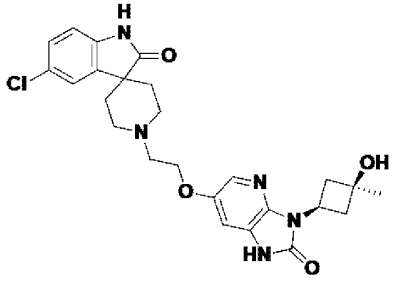
[1336] To a solution of (*cis*)-3-((5-(2-bromoethoxy)-3-nitropyridin-2-yl)amino)-1-methylcyclobutan-1-ol (300 mg, 867 μmol) in EtOH (5 mL) and H_2O (2.5 mL) was added Fe (484 mg, 8.67 mmol) and NH_4Cl (695 mg, 13.0 mmol). The mixture was stirred at 60 °C for 4 h. After cooling to room temperature, the mixture was filtered. The filtrate was diluted with H_2O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to provide (*cis*)-3-((3-amino-5-(2-bromoethoxy)pyridin-2-yl)amino)-1-methylcyclobutan-1-ol, which was used in the subsequent step without further purification. MS = 315.9 / 317.9 $[M+H]^+$.

Step 5: 6-(2-bromoethoxy)-3-((*cis*)-3-hydroxy-3-methylcyclobutyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one



[1337] To a solution of (*cis*)-3-((3-amino-5-(2-bromoethoxy)pyridin-2-yl)amino)-1-methylcyclobutan-1-ol (100 mg, 316 μmol) in THF (4 mL) was added CDI (103 mg, 633 μmol). The mixture was stirred at 60 °C for 16 h. After cooling to room temperature, the mixture was diluted with H_2O (10 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to provide 6-(2-bromoethoxy)-3-((*cis*)-3-hydroxy-3-methylcyclobutyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one, which was used in the subsequent step without further purification. MS= 341.9 / 343.9 $[M+H]^+$.

Step 6: 5-chloro-1'-[2-({2-oxo-3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H-imidazo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 374)

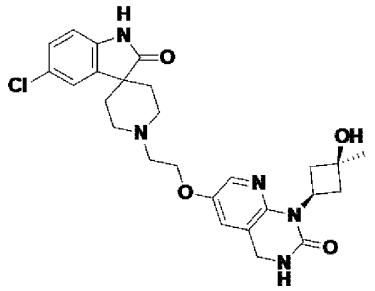


[1338] To a solution of 6-(2-bromoethoxy)-3-((*cis*)-3-hydroxy-3-methylcyclobutyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (100 mg, 292 μmol) in MeCN (3 mL) was added $NaHCO_3$ (98.2 mg, 1.17 mmol) and 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 79.8 mg, 292 μmol, HCl salt). The mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the mixture was concentrated in vacuo to remove MeCN. The residue was dissolved in DMF (1.5 mL) and was filtered to remove solids. The filtrate was purified by reverse phase preparative HPLC (Waters Xbridge OBD C_{18} column, 20–50% MeCN:10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-[2-({2-oxo-3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H-imidazo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 374**). ^1H NMR

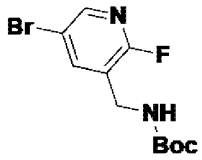
(400 MHz, DMSO-d_6): δ 11.04 (br s, 1H), 10.48 (s, 1H), 7.72 (d, J = 2.4 Hz, 1H), 7.49 (d, J = 1.8 Hz, 1H), 7.27 – 7.18 (m, 1H), 7.03 (d, J = 2.6 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 5.16 (s, 1H), 4.48 – 4.33 (m, 1H), 4.17 (t, J = 6.0 Hz, 2H), 3.08 – 2.98 (m, 2H), 2.96 – 2.88 (m, 2H), 2.84 (t, J = 6.0 Hz, 2H), 2.75 – 2.62 (m, 2H), 2.32 – 2.21 (m, 2H), 1.86 – 1.64 (m, 4H), 1.32 (s, 3H). MS= 498.1 $[M+H]^+$.

Example 86

(5-chloro-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H,4H-pyrido[2,3-d]pyrimidin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one, Compound 356)

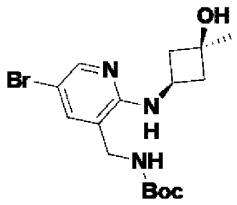


Step 1: *tert*-butyl *N*-[(5-bromo-2-fluoro-3-pyridyl)methyl]carbamate



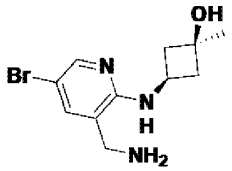
[1339] To a mixture of 5-bromo-2-fluoro-pyridine-3-carbaldehyde (5.00 g, 24.5 mmol) and *tert*-butyl carbamate (5.74 g, 49.0 mmol) in DCM (50 mL) under N_2 atmosphere was added TFA (5.44 mL, 73.5 mmol) and Et_3SiH (19.6 mL, 123 mmol). The mixture was stirred at room temperature for 16 h under N_2. The mixture was quenched by addition of saturated aqueous $NaHCO_3$ solution (130 mL) and extracted with DCM (2 x 100 mL). The combined organic layers were concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 80 g cartridge 0–8% EtOAc/Petroleum ether) to provide *tert*-butyl *N*-[(5-bromo-2-fluoro-3-pyridyl)methyl]carbamate. MS = 304.9 / 306.9 $[M+H]^+$.

Step 2: *tert*-butyl *N*-[(5-bromo-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}pyridin-3-yl)methyl]carbamate



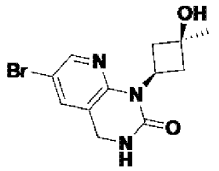
[1340] A mixture of *tert*-butyl *N*-[(5-bromo-2-fluoro-3-pyridyl)methyl]carbamate (3.80 g, 12.5 mmol), (*cis*)-3-amino-1-methylcyclobutanol (1.89 g, 13.7 mmol, HCl salt) and DIEA (41 mL, 249 mmol) in DMSO (20 mL) was stirred at 90 °C for 16 h under N_2 atmosphere. After cooling to room temperature, the mixture was diluted with H_2O (150 mL), and extracted with EtOAc (80 mL x 2). The combined organic layers were concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 40 g cartridge, 0–25% EtOAc/Petroleum ether) to provide *tert*-butyl *N*-[(5-bromo-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}pyridin-3-yl)methyl]carbamate. MS = 386.0 / 387.9 $[M+H]^+$.

Step 3: (*cis*)-3-{[3-(aminomethyl)-5-bromopyridin-2-yl]amino}-1-methylcyclobutan-1-ol



[1341] A solution of *tert*-butyl *N*-[(5-bromo-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}pyridin-3-yl)methyl]carbamate (1.50 g, 3.88 mmol) in 4.0 M HCl in EtOAc (15 mL, 60 mmol) was stirred at room temperature for 1 h. The mixture was concentrated in vacuo to give (*cis*)-3-{[3-(aminomethyl)-5-bromopyridin-2-yl]amino}-1-methylcyclobutan-1-ol, which was used in the subsequent step without further purification. MS = 285.9 / 287.8 $[M+H]^+$.

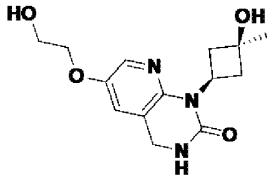
Step 4: 6-bromo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H,4H-pyrido[2,3-d]pyrimidin-2-one



[1342] To a mixture of (*cis*)-3-{[3-(aminomethyl)-5-bromopyridin-2-yl]amino}-1-methylcyclobutan-1-ol (1.20 g, 4.19 mmol) in THF (15 mL) was added CDI (1.02 g, 6.29 mmol).

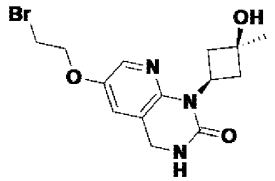
The mixture was stirred at room temperature for 1 h, then was diluted with brine (15 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give 6-bromo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H,4H-pyrido[2,3-d]pyrimidin-2-one, which was used in the subsequent step without further purification. MS = 312.0 / 313.9 $[M+H]^+$.

Step 5: 6-(2-hydroxyethoxy)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H,4H-pyrido[2,3-d]pyrimidin-2-one



[1343] A mixture of 6-bromo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H,4H-pyrido[2,3-d]pyrimidin-2-one (350 mg, 1.12 mmol), CuI (85.4 mg, 0.448 mmol), *t*-BuOLi (359 mg, 4.48 mmol) and ethylene glycol (4.17 mL, 74.5 mmol) was degassed and purged with N_2 for 10 min, and then stirred at 120 °C for 16 h under N_2 atmosphere. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated in vacuo. The filtrate was purified by reverse phase preparative HPLC (Waters Xbridge OBD C_{18} column, 1–30% MeCN:10 mM NH_4HCO_3 in H_2O) to give 6-(2-hydroxyethoxy)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H,4H-pyrido[2,3-d]pyrimidin-2-one. MS = 294.0 $[M+H]^+$.

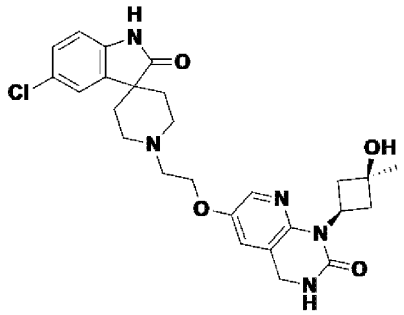
Step 6: 6-(2-bromoethoxy)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H,4H-pyrido[2,3-d]pyrimidin-2-one



[1344] To a mixture of 6-(2-hydroxyethoxy)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H,4H-pyrido[2,3-d]pyrimidin-2-one (180 mg, 0.614 mmol) in DCM (8 mL) at 0 °C under N_2 atmosphere was added PPh_3 (805 mg, 3.07 mmol), followed by CBr_4 (1.02 g, 3.07 mmol). The mixture was stirred at room temperature for 16 h under N_2 atmosphere, them was concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 4 g cartridge, 0–100%

EtOAc/Petroleum ether) to give 6-(2-bromoethoxy)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H,4H-pyrido[2,3-d]pyrimidin-2-one. MS = 356.0 / 357.9 $[M+H]^+$.

Step 7: 5-chloro-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H,4H-pyrido[2,3-d]pyrimidin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one



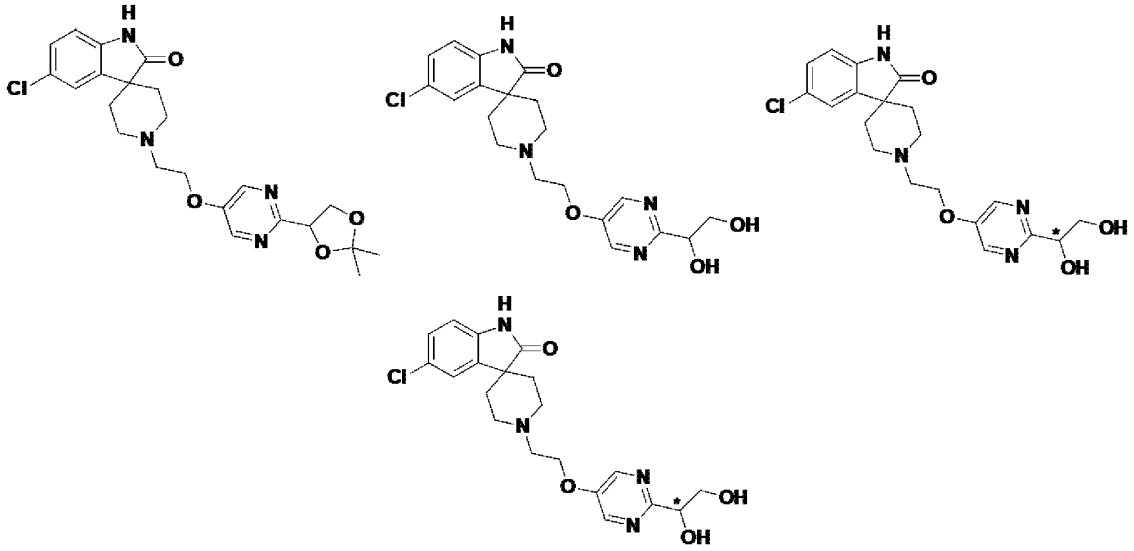
[1345] To a solution of 6-(2-bromoethoxy)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H,4H-pyrido[2,3-d]pyrimidin-2-one (50.0 mg, 0.140 mmol) in MeCN (4 mL) was added $NaHCO_3$ (47.2 mg, 0.561 mmol) and 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 38.3 mg, 0.140 mmol, HCl salt). The mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the mixture was concentrated in vacuo. The residue was purified by reverse phase preparative HPLC (Waters Xbridge OBD C_{18} column, 20–50% MeCN:10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H,2H,3H,4H-pyrido[2,3-d]pyrimidin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 356**). ^1H NMR (400 MHz, DMSO-d_6): δ 10.48 (br s, 1H), 7.90 (d, J = 2.8 Hz, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.34 (d, J = 2.8 Hz, 1H), 7.23 (dd, J = 8.4, 2.0 Hz, 1H), 7.11 (s, 1H), 6.84 (d, J = 8.4 Hz, 1H), 4.81 (s, 1H), 4.19 – 4.11 (m, 4H), 4.06 (t, J = 7.6 Hz, 1H), 2.96 – 2.87 (m, 2H), 2.83 (t, J = 5.6 Hz, 2H), 2.75 – 2.64 (m, 2H), 2.47 – 2.40 (m, 2H), 2.34 – 2.23 (m, 2H), 1.84 – 1.65 (m, 4H), 1.25 (s, 3H). MS = 512.4 $[M+H]^+$.

Example 87

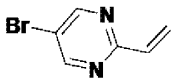
5-chloro-1'-(2-{[2-(2,2-dimethyl-1,3-dioxolan-4-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

5-chloro-1'-(2-{[2-(1,2-dihydroxyethyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

5-chloro-1'-[2-({2-[(1*R* or 1*S*)-1,2-dihydroxyethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
& 5-chloro-1'-[2-({2-[(1*S* or 1*R*)-1,2-dihydroxyethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
(Compounds 441, 330, 378, & 379)

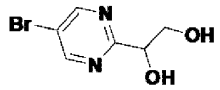


Step 1: 5-bromo-2-vinylpyrimidine



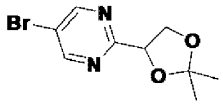
[1346] A mixture of 5-bromo-2-iodopyrimidine (5.00 g, 17.6 mmol), vinyl potassium trifluoroborate (2.59 g, 19.3 mmol), $Pd(dppf)Cl_2$ (1.28 g, 1.76 mmol), and K_2CO_3 (6.06 g, 43.9 mmol) in 1,4-dioxane (75 mL) and H_2O (25 mL) was degassed and purged with N_2 (3x), and then the mixture was stirred at 90 °C for 12 h under N_2 atmosphere. After cooling to room temperature, the reaction mixture was diluted with H_2O (60 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 40 g cartridge, 0–15% EtOAc/Petroleum ether) to give 5-bromo-2-vinylpyrimidine. MS = 185.10 $[M+H]^+$.

Step 2: 1-(5-bromopyrimidin-2-yl)ethane-1,2-diol



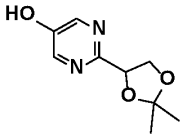
[1347] To a 0 °C solution of 5-bromo-2-vinyl-pyrimidine (1.80 g, 9.73 mmol) in THF (20 mL) and H_2O (20 mL) was added K_2OsO_4•$2H_2O$ (358 mg, 0.973 mmol) and NMO (2.05 mL, 19.5 mmol). The mixture was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by reverse phase preparative HPLC (Waters Xbridge OBD C_{18} column, 25–55% MeCN:10 mM NH_4HCO_3 in H_2O) to give 1-(5-bromopyrimidin-2-yl)ethane-1,2-diol. MS = 219.10 $[M+H]^+$.

Step 3: 5-bromo-2-(2,2-dimethyl-1,3-dioxolan-4-yl)pyrimidine



[1348] To a solution of 1-(5-bromopyrimidin-2-yl)ethane-1,2-diol (860 mg, 3.93 mmol) in acetone (9 mL) was added 2,2-dimethoxypropane (9.62 mL, 78.53 mmol) and TsOH (67.6 mg, 0.393 mmol). The mixture was stirred at room temperature for 16 h. The reaction mixture was with H_2O (20 mL) and extracted with EtOAc (4 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–70% EtOAc/Petroleum ether) to give 5-bromo-2-(2,2-dimethyl-1,3-dioxolan-4-yl)pyrimidine. MS = 259.0 $[M+H]^+$.

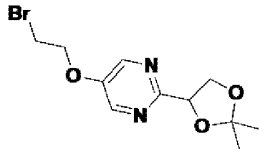
Step 4: 2-(2,2-dimethyl-1,3-dioxolan-4-yl)pyrimidin-5-ol



[1349] A mixture of 5-bromo-2-(2,2-dimethyl-1,3-dioxolan-4-yl)pyrimidine (200 mg, 0.772 mmol), $Pd(dba)_2$ (8.88 mg, 15.4 μmol), ditert-butyl-[2,3,4,5-tetramethyl-6-(2,4,6-triisopropylphenyl)phenyl]phosphane (37.1 mg, 77.2 μmol) and KOH (129.92 mg, 2.32 mmol) in H_2O (2 mL) and 1,4-dioxane (5 mL) was degassed and purged with N_2 (3x), and then the mixture was stirred at 100 °C for 16 h under N_2 atmosphere. After cooling to room temperature, the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x

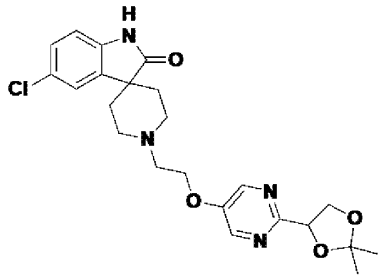
10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give 2-(2,2-dimethyl-1,3-dioxolan-4-yl)pyrimidin-5-ol), which was used in the subsequent step without further purification. MS = 197.1 $[M+H]^+$.

Step 5: 5-(2-bromoethoxy)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)pyrimidine



[1350] To a solution of 2-(2,2-dimethyl-1,3-dioxolan-4-yl)pyrimidin-5-ol (260 mg, 1.33 mmol) in MeCN (3 mL) and 1,2-dibromoethane (5 mL) under N_2 atmosphere was added K_2CO_3 (916 mg, 6.63 mmol). The mixture was stirred at 80 °C for 16 h under N_2 atmosphere. The reaction mixture was diluted with H_2O (30 mL) and extracted with DCM (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give 5-(2-bromoethoxy)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)pyrimidine, which was used in the subsequent step without further purification. MS = 303.2 / 305.2 $[M+H]^+$.

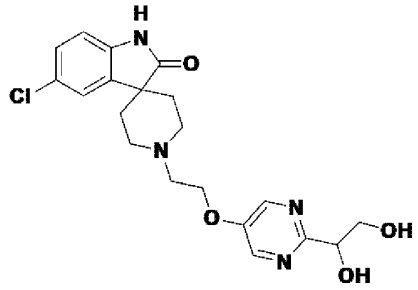
Step 6: 5-chloro-1'-(2-{[2-(2,2-dimethyl-1,3-dioxolan-4-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 441)



[1351] To a solution of 5-(2-bromoethoxy)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)pyrimidine (120 mg, 396 µmol) in MeCN (2 mL) under N_2 atmosphere was added $NaHCO_3$ (166 mg, 1.98 mmol) and 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4,** 112 mg, 475 µmol, HCl salt). The mixture was stirred at 80 °C for 12 h under N_2 atmosphere. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated in vacuo to afford 5-chloro-1'-(2-{[2-(2,2-dimethyl-1,3-dioxolan-4-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-

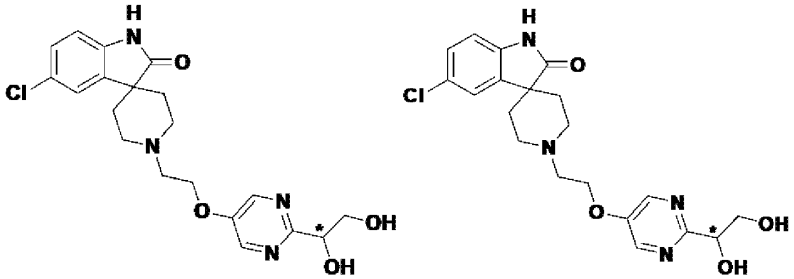
dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 441**), which was used in the subsequent step without further purification. MS = 459.2 $[M+H]^+$.

Step 7: 5-chloro-1'-(2-{[2-(1,2-dihydroxyethyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 330)



[1352] To a 0 °C solution of 5-chloro-1'-(2-{[2-(2,2-dimethyl-1,3-dioxolan-4-yl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 441**, 160 mg, 349 μmol) in THF (0.5 mL) was added 12 M aqueous HCl (0.20 mL, 2.4 mmol). The mixture was stirred at 0 °C for 2 h. The reaction mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified by reverse phase preparative HPLC (Waters Xbridge BEH C_{18} column, 15–40% MeCN:10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-(2-{[2-(1,2-dihydroxyethyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 330**). MS = 419.3 $[M+H]^+$.

Step 8: 5-chloro-1'-[2-({2-[(1*R* or 1*S*)-1,2-dihydroxyethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one
& 5-chloro-1'-[2-({2-[(1*S* or 1*R*)-1,2-dihydroxyethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compounds 378 & 379)

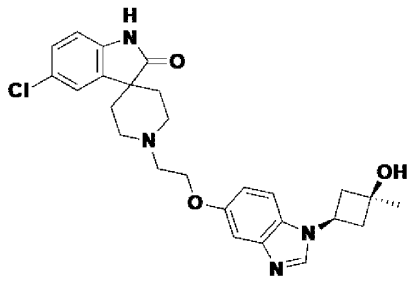


[1353] 5-chloro-1'-(2-{[2-(1,2-dihydroxyethyl)pyrimidin-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 330**) was separated by preparative chiral

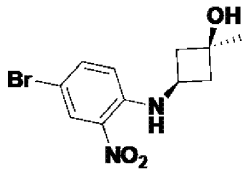
SFC (Chiralcel IF column, 30–80% Heptane:(4:1 EtOH:MeCN) with 0.1% NH_4OH in CO_2). The first eluting enantiomer of the title compound, 5-chloro-1'-[2-({2-[(1*R* or 1*S*)-1,2-dihydroxyethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 379**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.50 (s, 1H), 8.56 (s, 2H), 7.51 (s, 1H), 7.24 (dd, J = 7.6, 2.0 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 5.14 (d, J = 2.0 Hz, 1H), 4.62 – 4.59 (m, 2H), 4.30 (t, J = 5.6 Hz, 2H), 3.71 – 3.70 (m, 1H), 3.64 – 3.63 (m, 1H), 2.92 – 2.86 (m, 4H), 2.70 – 2.67 (m, 2H), 1.78 – 1.72 (m, 4H). MS = 419.30 $[M+H]^+$. The second eluting enantiomer of the title compound, 5-chloro-1'-[2-({2-[(1*S* or 1*R*)-1,2-dihydroxyethyl]pyrimidin-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 378**): ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.50 (s, 1H), 8.56 (s, 2H), 7.51 (s, 1H), 7.24 (dd, J = 8.0, 2.0 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 5.14 (d, J = 2.0 Hz, 1H), 4.62 – 4.59 (m, 2H), 4.30 (t, J = 5.6 Hz, 2H), 3.71 – 3.70 (m, 1H), 3.64 – 3.63 (m, 1H), 2.92 – 2.86 (m, 4H), 2.70 – 2.67 (m, 2H), 1.78 – 1.72 (m, 4H). MS = 419.30 $[M+H]^+$.

Example 88

5-chloro-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 351)



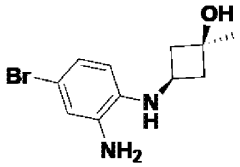
Step 1: (*cis*)-3-[(4-bromo-2-nitrophenyl)amino]-1-methylcyclobutan-1-ol



[1354] A mixture of 4-bromo-1-fluoro-2-nitro-benzene (1.96 mL, 15.9 mmol), (*cis*)-3-amino-1-methylcyclobutan-1-ol (2.41 g, 17.5 mmol, HCl salt) and DIEA (8.31 mL, 47.7 mmol) in DMSO (25 mL) under N_2 atmosphere was stirred at 90 °C for1 h. After cooling to room temperature, the

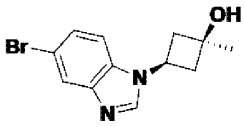
reaction mixture was quenched by addition of saturated aqueous NH_4Cl solution (150 mL). The mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give (*cis*)-3-[(4-bromo-2-nitrophenyl)amino]-1-methylcyclobutan-1-ol, which was used in the subsequent step without further purificaiton. MS = 300.9 / 302.9 $[M+H]^+$.

Step 2: (*cis*)-3-[(2-amino-4-bromophenyl)amino]-1-methylcyclobutan-1-ol



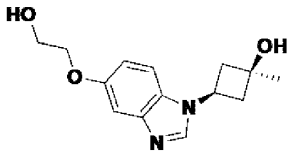
[1355] To a solution of (*cis*)-3-[(4-bromo-2-nitrophenyl)amino]-1-methylcyclobutan-1-ol (300 mg, 996 μmol) in EtOH (5 mL) and H_2O (2.5 mL) was added Fe (556 mg, 9.96 mmol) and NH_4Cl (799 mg, 14.9 mmol. The mixture was stirred at 60 °C for 2 h. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated in vacuo to afford (*cis*)-3-[(2-amino-4-bromophenyl)amino]-1-methylcyclobutan-1-ol, which was used in the subsequent step without further purification. MS = 270.9 / 272.9 $[M+H]^+$.

Step 3: (*cis*)-3-(5-bromo-1H-1,3-benzodiazol-1-yl)-1-methylcyclobutan-1-ol



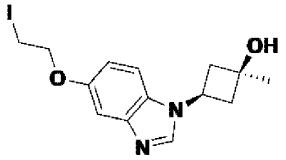
[1356] To a solution of (*cis*)-3-[(2-amino-4-bromophenyl)amino]-1-methylcyclobutan-1-ol (1.00 g, 3.69 mmol) in triethoxymethane (6.13 mL, 36.9 mmol) was added TsOH (63.5 mg, 369 μmol). The mixture was stirred at 80 °C for 4 h. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated in vacuo to give (*cis*)-3-(5-bromo-1H-1,3-benzodiazol-1-yl)-1-methylcyclobutan-1-ol, which was used in the subsequent step without further purification. MS = 281.0 / 283.0 $[M+H]^+$.

Step 4: (*cis*)-3-[5-(2-hydroxyethoxy)-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol



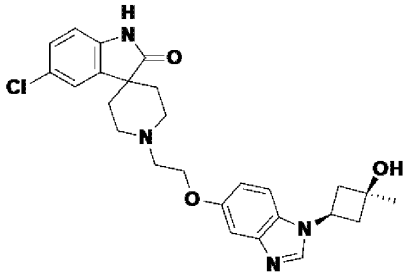
[1357] To a solution of (*cis*)-3-(5-bromo-1H-1,3-benzodiazol-1-yl)-1-methylcyclobutan-1-ol (1.30 g, 4.62 mmol) in ethylene glycol (15 mL) was added $CuCl_2$ (124 mg, 925 μmol) and K_2CO_3 (1.92 g, 13.9 mmol). The mixture was degassed and purged with N_2 for 10 min, and then stirred at 130 °C for 6 h. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by reverse phase preparative HPLC (Phenomenex Luna C_{18} column, 1–30% MeCN:10 mM NH_4HCO_3 in H_2O) to give (*cis*)-3-[5-(2-hydroxyethoxy)-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol. MS = 263.1 $[M+H]^+$.

Step 5: (*cis*)-3-[5-(2-iodoethoxy)-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol



[1358] To a solution of (*cis*)-3-[5-(2-hydroxyethoxy)-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol (200 mg, 762 μmol) in DCM (5 mL) was added I_2 (169 μL, 839 μmol), imidazole (104 mg, 1.52 mmol), and PPh_3 (220 mg, 839 μmol). The mixture was stirred at room temperature for 4 h. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified by preparative TLC (SiO_2, DCM:MeOH = 10:1) to give (*cis*)-3-[5-(2-iodoethoxy)-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol. MS = 373.0 $[M+H]^+$.

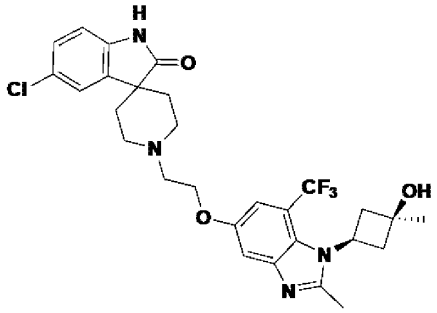
Step 6: 5-chloro-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 351)



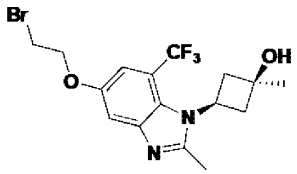
[1359] To a solution of (*cis*)-3-[5-(2-iodoethoxy)-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol (40.0 mg, 107 µmol) in MeCN (2 mL) was added 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4,** 32.3 mg, 118 µmol, HCl salt) and $NaHCO_3$ (36.1 mg, 430 µmol). The mixture was stirred at 80 °C for 12 h. After cooling to room temperature, the reaction mixture was quenched by addition of H_2O (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by reverse phase preparative HPLC (Phenomenex Luna C_{18}, 5–20% MeCN in H_2O with 0.2% formic acid modifier) to give 5-chloro-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 351**, formic acid salt). ^1H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 1H), 8.22 (s, 1H), 8.18 (s, 1H), 7.69 – 7.46 (m, 2H), 7.32 – 7.13 (m, 2H), 7.01 – 6.77 (m, 2H), 4.58 (t, J = 8.4 Hz, 1H), 4.16 (t, J = 5.6 Hz, 2H), 3.00 – 2.84 (m, 4H), 2.77 – 2.58 (m, 4H), 2.56 – 2.51 (m, 2H), 1.90 – 1.67 (m, 4H), 1.37 (s, 3H). MS = 481.3 $[M+H]^+$.

Example 89

5-chloro-1'-[2-({2-methyl-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 442)

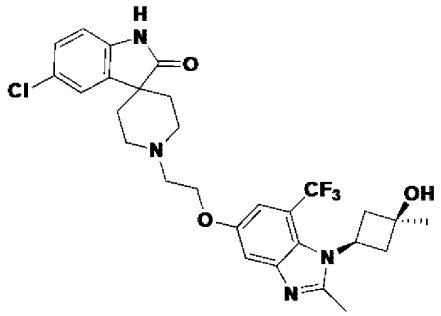


Step 1: (*cis*)-3-[5-(2-bromoethoxy)-2-methyl-7-(trifluoromethyl)-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol



[1360] To a mixture of 2-methyl-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-ol (**Intermediate A-119**, 1.40 g, 4.66 mmol) and 1,2-dibromoethane (17.5 g, 93.2 mmol) in *i*-PrOH (10 mL) was added Cs_2CO_3 (3.80 g, 11.7 mmol). The mixture was stirred at 60 °C for 2 h. After cooling to room temperature, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 20 g cartridge, 0–100% EtOAc/Petroleum ether) to give (*cis*)-3-[5-(2-bromoethoxy)-2-methyl-7-(trifluoromethyl)-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol. MS = 407.1 / 409.1 $[M+H]^+$.

Step 2: 5-chloro-1'-[2-({2-methyl-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

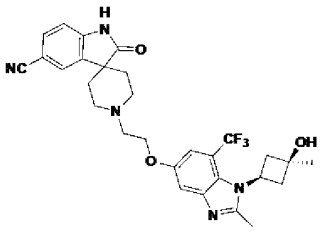
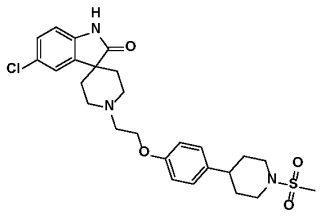
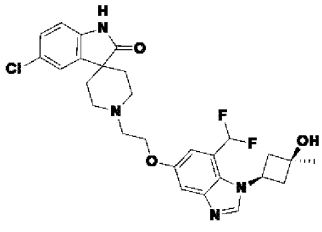


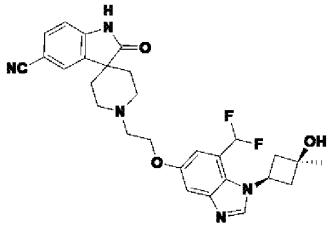
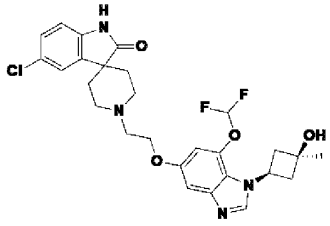
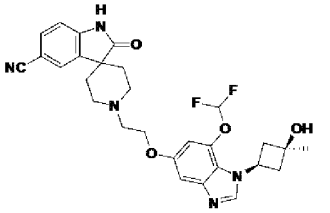
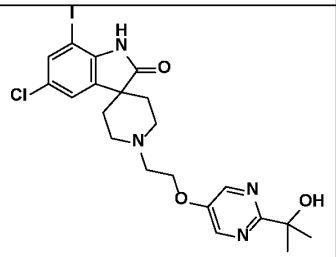
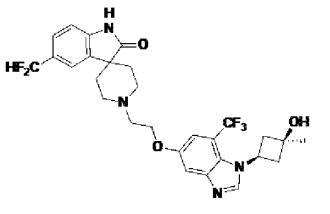
[1361] To a mixture of (*cis*)-3-[5-(2-bromoethoxy)-2-methyl-7-(trifluoromethyl)-1H-1,3-benzodiazol-1-yl]-1-methylcyclobutan-1-ol (150 mg, 368 mmol) and 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4,** 121 mg, 442 mmol, HCl salt) in MeCN (4 mL) was added $NaHCO_3$ (92.8 mg, 1.11 mmol). The mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase preparative HPLC (Waters Xbridge OBD C_{18} column, 30–60% MeCN:10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-[2-({2-methyl-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 442**). ^1H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1 H), 7.51 – 7.48 (m, 1 H), 7.47 – 7.43 (m, 1H), 7.23 (dd, J = 8.0, 2.0 Hz, 1H), 7.18 (d, J = 2.0 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 5.43 (s, 1H), 4.81 – 4.69 (m, 1H), 4.22 (t, J = 5.6 Hz, 2H), 2.97 – 2.90 (m, 2H), 2.90 – 2.86 (m, 2H), 2.85 (s, 3H), 2.83 – 2.76 (m, 2H), 2.73 – 2.70

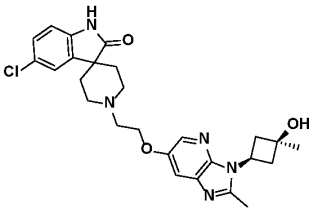
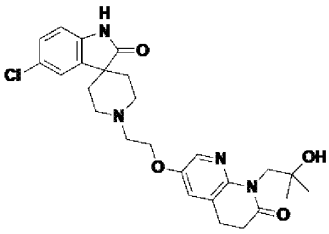
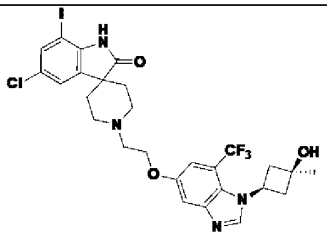
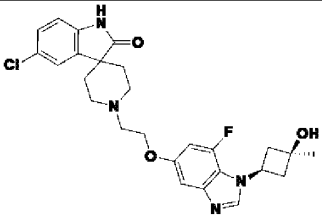
(m, 2H), 2.46 – 2.45 (m, 2H), 1.83 – 1.75 (m, 2 H), 1.74 – 1.66 (m, 2 H), 1.34 (s, 3 H). MS = 563.1 $[M+H]^+$.

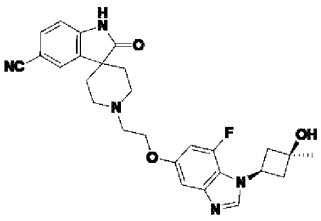
[1362] The following intermediates in **Table 38.16** were prepared according to procedures analogous to those described for **Compound 442** using the appropriate starting materials or common intermediates.

Table 38.16

#	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Intermed-iates Used
443		1'-[2-({2-methyl-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 554.2 Found 554.2	**A-119 and B-9**
444		5-chloro-1'-{2-[4-(1-methanesulfonylpiperidin-4-yl)phenoxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 518.2 Found 518.2	**General Procedure for Intermediate A-104, Step 2 and B-4**
445		5-chloro-1'-(2-{[7-(difluoromethyl)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 531.2 Found 531.2	**A-120 and B-4**

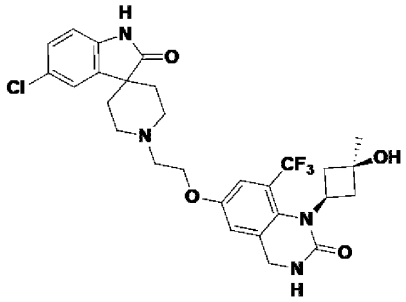
446		1'-(2-{[7-(difluoromethyl)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 522.2 Found 522.2	**A-120 and B-9**
447		5-chloro-1'-(2-{[7-(difluoromethoxy)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 547.2 Found 547.3	**A-121 and B-4**
448		1'-(2-{[7-(difluoromethoxy)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 538.2 Found 538.3	**A-121 and B-9**
449		5-chloro-1'-(2-((2-(2-hydroxypropan-2-yl)pyrimidin-5-yl)oxy)ethyl)-7-iodospiro[indoline-3,4'-piperidin]-2-one	Calc'd 543.1 Found 543.2	**A-100 and B-24**
450		5-(difluoromethyl)-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-	Calc'd 565.2 Found 565.2	**A-92 and B-1**

		1,2-dihydrospiro[indole-3,4'-piperidin]-2-one		
451		5-chloro-1'-[2-({2-methyl-3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-3H-imidazo[4,5-b]pyridin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 496.2 Found 496.2	**A-122 and B-4**
452		5-chloro-1'-(2-{[8-(2-hydroxy-2-methylpropyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 499.2 Found 499.2	**A-105 and B-4**
453		5-chloro-7-iodo-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one	Calc'd 675.1 Found 675.0	**A-92 and B-24**
454		5-chloro-1'-(2-((7-fluoro-1-((*cis*)-3-hydroxy-3-methylcyclobutyl)-1H-benzo[d]imidazol-5-yl)oxy)ethyl)spiro[indoline-3,4'-piperidin]-2-one	Calc'd 499.2 Found 499.2	**A-124 and B-4**

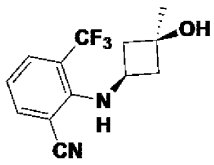
455		1'-(2-((7-fluoro-1-((*cis*)-3-hydroxy-3-methylcyclobutyl)-1H-benzo[d]imidazol-5-yl)oxy)ethyl)-2-oxospiro[indoline-3,4'-piperidine]-5-carbonitrile	Calc'd 490.2 Found 490.2	**A-124 and B-9**

Example 90

5-chloro-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinazolin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 456)

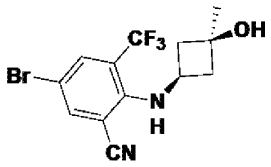


Step 1: 2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}-3-(trifluoromethyl)benzonitrile



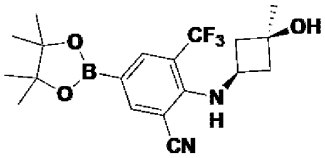
[1363] To a solution of (*cis*)-3-amino-1-methylcyclobutanol (12.0 g, 87.3 mmol, HCl salt) in DMSO (150 mL) was added 2-fluoro-3-(trifluoromethyl)benzonitrile (15.0 g, 79.3 mmol) and DIEA (30.8 g, 238 mmol). The mixture was stirred at 60 °C for 6 h. After cooling to room temperature, the reaction mixture was quenched by addition of H_2O (200 mL) and extracted with EtOAc (3 x 80 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 40 g cartridge, 0–10% EtOAc/Petroleum ether) to give 2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}-3-(trifluoromethyl)benzonitrile. MS = 271.1 $[M+H]^+$.

Step 2: 5-bromo-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}-3-(trifluoromethyl)benzonitrile



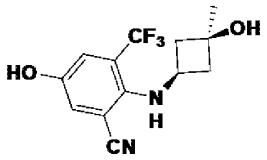
[1364] To a solution of 2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}-3-(trifluoromethyl)benzonitrile (12.0 g, 44.4 mmol) in DMF (150 mL) was added NBS (10.3 g, 57.7 mmol). The mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was quenched by addition of H_2O (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 80 g cartridge, 0–15% EtOAc/Petroleum ether) to give 5-bromo-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}-3-(trifluoromethyl)benzonitrile. MS = 349.0 / 351.0 $[M+H]^+$.

Step 3: 2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)benzonitrile



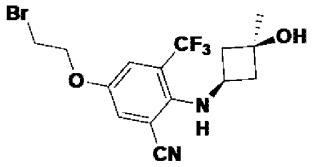
[1365] To a solution of 5-bromo-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}-3-(trifluoromethyl)benzonitrile (9.00 g, 25.8 mmol) in 1,4-dioxane (150 mL) was added KOAc (6.32 g, 64.4 mmol), bis(pinacolato)diboron (6.55 g, 25.8 mm*ol)* and $Pd(dppf)Cl_2$ (1.89 g, 2.58 mmol). The mixture was degassed and purged with N_2 (3x), then stirred at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give 2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)benzonitrile, which was taken to the next step without further purification. MS = 397.1 $[M+H]^+$.

Step 4: 5-hydroxy-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}-3-(trifluoromethyl)benzonitrile



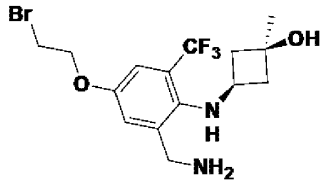
[1366] To a solution of 2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)benzonitrile (15.0 g, 22.7 mmol, 60% purity) in THF (90 mL) and H_2O (30 mL) was added Oxone (13.9 g, 22.7 mmol). The mixture was stirred at room temperature for 2 h. The reaction mixture was quenched by addition of saturated aqueous Na_2SO_3 (100 ml) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 80 g cartridge, 0–37% EtOAc/Petroleum ether) to give 5-hydroxy-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}-3-(trifluoromethyl)benzonitrile. MS = 287.1 $[M+H]^+$

Step 5: 5-(2-bromoethoxy)-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}-3-(trifluoromethyl)benzonitrile



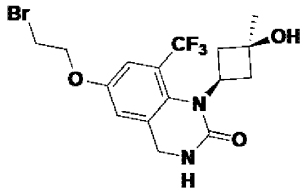
[1367] To a solution of 5-hydroxy-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}-3-(trifluoromethyl)benzonitrile (6.00 g, 20.9 mmol) in 1,2-dibromoethane (63.3 mL, 838 mmol) and MeCN (20 mL) was added K_2CO_3 (14.5 g, 105 mmol). The mixture was stirred at 80 °C for 12 h. After cooling to room temperature, solids were removed by filtration. H_2O (80 mL) was then added to the filtrate, and the mixture was extracted with DCM (3 x 60 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 40 g cartridge, 0–15% EtOAc/Petroleum ether) to give 5-(2-bromoethoxy)-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}-3-(trifluoromethyl)benzonitrile. MS = 393.0 / 395.0 $[M+H]^+$.

Step 6: (*cis*)-3-{[2-(aminomethyl)-4-(2-bromoethoxy)-6-(trifluoromethyl)phenyl]amino}-1-methylcyclobutan-1-ol



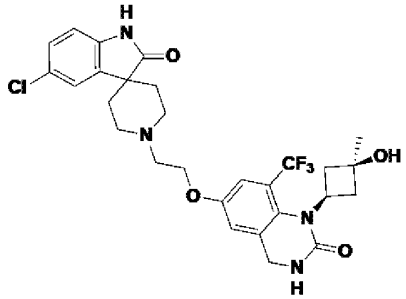
[1368] To a mixture of 5-(2-bromoethoxy)-2-{[(*cis*)-3-hydroxy-3-methylcyclobutyl]amino}-3-(trifluoromethyl)benzonitrile (3.00 g, 7.63 mmol) in THF (50 mL) at 0 °C was added 10 M BH_3•Me_2S in Me_2S (2.29 mL. 22.9 mmol). The mixture was then stirred at 60 °C for 5 h. After cooling to room temperature, the reaction mixture was quenched by addition of MeOH (30 mL) and H_2O (20 mL), then extracted with EtOAc (3 x 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give (*cis*)-3-{[2-(aminomethyl)-4-(2-bromoethoxy)-6-(trifluoromethyl)phenyl]amino}-1-methylcyclobutan-1-ol, which was taken to the next step without further purification. MS = 397.0 / 399.0 $[M+H]^+$.

Step 7: 6-(2-bromoethoxy)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinazolin-2-one



[1369] To a solution of (*cis*)-3-{[2-(aminomethyl)-4-(2-bromoethoxy)-6-(trifluoromethyl)phenyl]amino}-1-methylcyclobutan-1-ol (200 mg, 503 μmol) in THF (5 mL) was added CDI (245 mg, 1.51 mmol). The mixture was stirred at 60 °C for 5 h. After cooling to room temperature, the reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (SiO_2, 100% EtOAc) to give 6-(2-bromoethoxy)-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinazolin-2-one. MS = 423.0 / 425.0 $[M+H]^+$.

Step 8: 5-chloro-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinazolin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

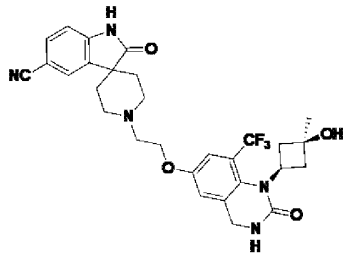


[1370] To a solution of 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4,** 51.6 mg, 189 μmol, HCl salt) in MeCN (2 mL) was added 6-(2-bromoethoxy)-1-(3-hydroxy-3-methyl-cyclobutyl)-8-(trifluoromethyl)-3,4-dihydroquinazolin-2-one (80.0 mg, 189 μmol) and $NaHCO_3$ (63.5 mg, 756 μmol). The mixture was stirred at 80 °C for 5 h under N_2 atmosphere. The mixture was then diluted with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL**)**. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The filtrate was purified by reverse phase preparative HPLC (Phenomenex Luna C_{18} column, 10–30% MeCN:0.04% HCl in H_2O) to give 5-chloro-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinazolin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 456)**. ^{1}H NMR (400 MHz, DMSO-d_6, HCl salt): δ 10.96 – 10.66 (m, 1.5H), 10.30 (s, 0.5H), 7.99 (s, 1H), 7.35 – 7.31 (m, 1H), 7.30 – 7.27 (m, 1H), 7.26 – 7.15 (m, 2H), 6.91 (dd, J = 8.0, 14.0 Hz, 1H), 5.32 – 4.67 (m, 1H), 4.49 (d, J = 4.0 Hz, 2H), 4.13 (s, 2H), 3.87 – 3.55 (m, 7H), 2.55 – 2.51 (m, 1H), 2.39 – 2.28 (m, 2H), 2.24 – 2.12 (m, 1H), 2.06 – 1.86 (m, 4H), 1.16 (s, 3H). MS = 579.1 $[M+H]^+$.

[1371] The following compounds in **Table 38.17** were prepared according to procedures similar to steps described for **Example 90** using the appropriate starting materials or common intermediates.

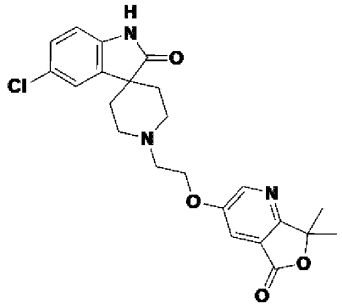
Table 38.17

#	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Intermediates used

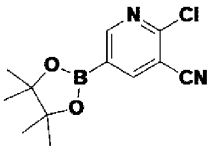
457		2-oxo-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-8-(trifluoromethyl)-1,2,3,4-tetrahydroquinazolin-6-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 570.2 Found 570.1	**B-9**

Example 91

5-chloro-1'-[2-({7,7-dimethyl-5-oxo-5H,7H-furo[3,4-b]pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 458)

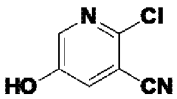


Step 1: 2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carbonitrile



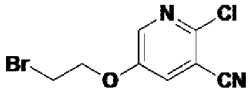
[1372] A mixture of 5-bromo-2-chloro-pyridine-3-carbonitrile (10.0 g, 46.0 mmol), bis(pinacolato)diboron (17.5 g, 69.0 mmol), KOAc (11.3 g, 115 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (1.88 g, 2.30 mmol) in 1,4-dioxane (100 mL) was degassed and purged with N_2 (3x), and then the mixture was stirred at 90 °C for 12 h under N_2 atmosphere. After cooling to room temperature, solids were removed by filtration, and then the mixture concentrated in vacuo give 2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carbonitrile, which was taken to the next step without further purification.

Step 2: 2-chloro-5-hydroxypyridine-3-carbonitrile



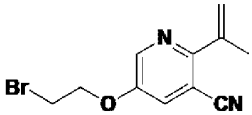
[1373] To a solution of 2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carbonitrile (1.30 g, 4.91 mmol) in THF (10 mL) and H_2O (4 mL) was added Oxone (2.42 g, 3.93 mmol). The mixture was stirred at 0 °C for 1 h, then was quenched with saturated aqueous Na_2SO_3 solution (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–30% EtOAc/Petroleum ether) to provide 2-chloro-5-hydroxypyridine-3-carbonitrile. MS = 155.1 $[M+H]^+$.

Step 3: 5-(2-bromoethoxy)-2-chloropyridine-3-carbonitrile



[1374] To a solution of 2-chloro-5-hydroxypyridine-3-carbonitrile (550 mg, 3.56 mmol) in MeCN (7 mL) was added K_2CO_3 (2.46 g, 17.8 mmol) and 1,2-dibromoethane (20.1 g, 107 mmol). The mixture was stirred at 80 °C for 12 h. After cooling to room temperature, the solids were removed by filtration and the filtrate was concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–30% EtOAc/Petroleum ether) to provide 5-(2-bromoethoxy)-2-chloropyridine-3-carbonitrile. MS = 260.9 / 262.9 $[M+H]^+$.

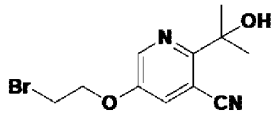
Step 4: 5-(2-bromoethoxy)-2-(prop-1-en-2-yl)pyridine-3-carbonitrile



[1375] A mixture of 5-(2-bromoethoxy)-2-chloropyridine-3-carbonitrile (300 mg, 1.15 mmol), 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (386 mg, 2.29 mmol), Cs_2CO_3 (1.87 g, 5.74 mmol) and $Pd(PPh_3)Cl_2$ (8.05 mg, 11.5 μmol) in 1,4-dioxane (3 mL) and H_2O (0.5 mL) was degassed and purged with N_2 (3x), and then the mixture was stirred at 100 °C for 2 h under N_2 atmosphere. After cooling to room temperature, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel

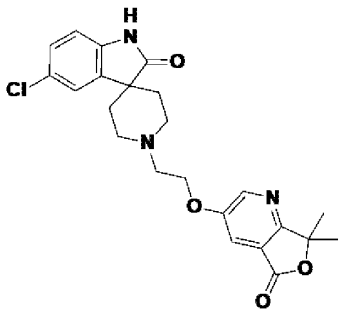
chromatography (Biotage 12 g cartridge, 0–20% EtOAc/Petroleum ether) to give 5-(2-bromoethoxy)-2-(prop-1-en-2-yl)pyridine-3-carbonitrile. MS = 267.0 / 269.0 $[M+H]^+$.

Step 5: 5-(2-bromoethoxy)-2-(2-hydroxypropan-2-yl)pyridine-3-carbonitrile



[1376] A mixture of 5-(2-bromoethoxy)-2-(prop-1-en-2-yl)pyridine-3-carbonitrile (100 mg, 374 μmol), tris(2,2,6,6-tetramethyl-3,5-heptanedionato)manganese(III) (22.6 mg, 37.4 μmol), and phenylsilane (81.0 mg, 749 μmol) in DCM (0.5 mL) and *i*-PrOH (10 mL) was degassed and purged with O_2 (3x), and then the mixture was stirred at 0 °C for 2 h under O_2 atmosphere. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage 4 g cartridge, 0–40% EtOAc/Petroleum ether) to give 5-(2-bromoethoxy)-2-(2-hydroxypropan-2-yl)pyridine-3-carbonitrile. MS = 285.0 / 286.9 $[M+H]^+$.

Step 6: 5-chloro-1'-[2-({7,7-dimethyl-5-oxo-5H,7H-furo[3,4-b]pyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

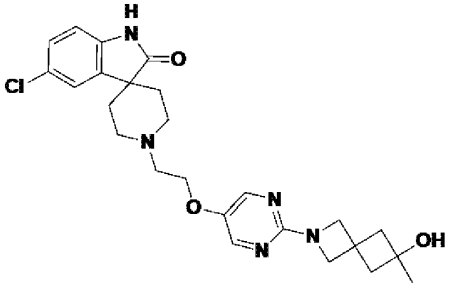


[1377] To a solution of 5-(2-bromoethoxy)-2-(2-hydroxypropan-2-yl)pyridine-3-carbonitrile (100 mg, 351 μmol) and 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 105 mg, 386 μmol, HCl salt) in MeCN (3 mL) was added $NaHCO_3$ (88.4 mg, 1.05 mmol). The mixture was stirred at 80 °C for 12 h. After cooling to room temperature, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The filtrate was purified by reverse phase preparative HPLC (Phenomenex Luna C_{18} column, 20–50% MeCN:10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-[2-({7,7-dimethyl-5-oxo-5H,7H-furo[3,4-b]pyridin-3-yl}oxy)ethyl]-1,2-

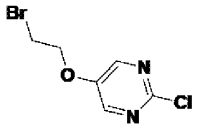
dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 458**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 1H), 8.64 (d, J = 2.8 Hz, 1H), 7.78 (d, J = 2.4 Hz, 1H), 7.50 (d, J = 1.6 Hz, 1H), 7.24 (dd, J = 8.0, 2.0 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 4.33 (t, J = 5.6 Hz, 2H), 2.96 – 2.86 (m, 4H), 2.74 – 2.67 (m, 2H), 1.82 – 1.67 (m, 4H), 1.61 (s, 6H). MS = 442.3 $[M+H]^+$.

Example 92

5-chloro-1'-{2-[(2-{6-hydroxy-6-methyl-2-azaspiro[3.3]heptan-2-yl}pyrimidin-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 459)

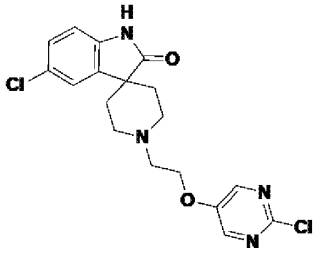


Step 1: 5-(2-bromoethoxy)-2-chloropyrimidine



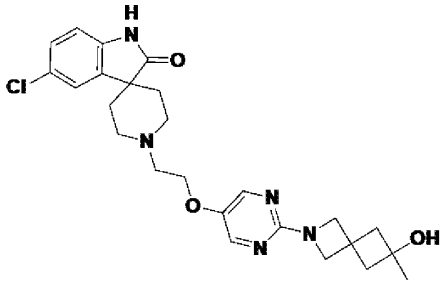
[1378] To a solution of 2-chloropyrimidin-5-ol (1.00 g, 7.66 mmol) in DMF (7.661 mL) was added 1,2-dibromoethane (15.3 mL) and Cs_2CO_3 (7.49 g, 23.0 mmol). The reaction was heated at 90 °C for 16 h. The reaction was cooled to room temperature, diluted with EtOAc (30 mL), and filtered through a pad of Celite. The filtrate was concentrated, and the residue was purified by flash silica gel chromatography (Biotage 50 g cartridge, 0–100% EtOAc/Hexanes) to provide 5-(2-bromoethoxy)-2-chloropyrimidine. MS = 236.96 $[M+H]^+$.

Step 2: 5-chloro-1'-{2-[(2-chloropyrimidin-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one



[1379] To a vial was added 5-(2-bromoethoxy)-2-chloropyrimidine (1.23 g, 5.18 mmol), 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 1.34 g, 4.92 mmol, HCl salt), K_2CO_3 (2.15 g, 15.5 mmol), and KI (860 mg, 5.18 mmol) followed by DMF (17.3 mL). The mixture was heated at 65 °C for 4 h. The reaction was cooled to room temperature and diluted with H_2O (100 mL). The resulting precipitate was collected by filtration and dried in vacuo to provide 5-chloro-1'-{2-[(2-chloropyrimidin-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one, which was used in the subsequent step without further purification. MS = 393.2 $[M+H]^+$.

Step 3: 5-chloro-1'-{2-[(2-{6-hydroxy-6-methyl-2-azaspiro[3.3]heptan-2-yl}pyrimidin-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

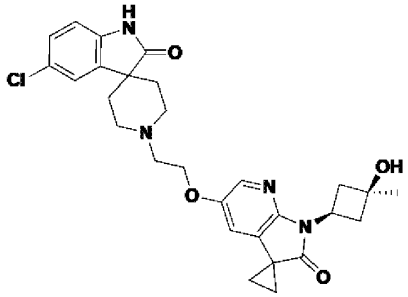


[1380] To a solution of 5-chloro-1'-{2-[(2-chloropyrimidin-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (75.0 mg, 0.191 mmol) and 6-methyl-2-azaspiro[3.3]heptan-6-ol (156 mg, 0.954 mmol, HCl salt) in DMSO (0.381 mL) was added triethylamine (0.132 mL, 0.954 mmol). The reaction was heated at 100 °C under microwave irradiation for 1 h. After cooling to room temperature, the mixture was diluted with H_2O (1 mL) and MeCN (1 mL). The resulting solution was purified by reverse phase preparative HPLC (Phenomenex Kinetex C_{18} column, 5–50% MeCN in H_2O with 0.1% NH_4OH modifier) to give 5-chloro-1'-{2-[(2-{6-hydroxy-6-methyl-2-azaspiro[3.3]heptan-2-yl}pyrimidin-5-yl)oxy]ethyl}-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one **(Compound 459)**. ^1H NMR (500 MHz, DMSO-d_6,

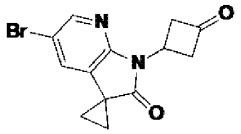
29/30H): δ 10.41 (s, 1H), 8.15 – 8.06 (m, 2H), 7.42 (d, *J* = 2.1 Hz, 1H), 7.16 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 4.82 (s, 1H), 4.27 – 4.02 (m, 2H), 3.94 – 3.77 (m, 4H), 2.87 – 2.77 (m, 2H), 2.73 (t, *J* = 5.7 Hz, 2H), 2.65 – 2.55 (m, 2H), 2.16 – 2.07 (m, 3H), 1.77 – 1.57 (m, 4H), 1.12 (s, 3H). MS = 484.28 $[M+H]^+$.

Example 93

5-chloro-1'-(2-{2'-oxo-1'-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-5'-yloxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 460)

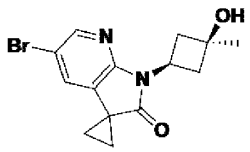


Step 1: 5'-bromo-1'-(3-oxocyclobutyl)spiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-2'-one



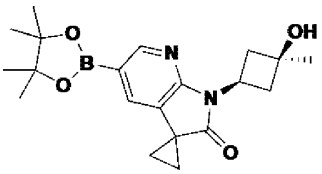
[1381] To a solution of 5'-bromo-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-2'-one (600 mg, 2.51 mmol) in DMF (8.37 mL) was added K_2CO_3 (1.04 g, 7.53 mmol) followed by 3-bromocyclobutan-1-one (0.56 g, 3.77 mmol). The reaction was allowed to stir at room temperature for 3 h, then was diluted with H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and then concentrated in vacuo to give 5'-bromo-1'-(3-oxocyclobutyl)-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-2'-one which was used in the subsequent step without further purification. MS = 307.02 $[M+H]^+$.

Step 2: 5'-bromo-1'-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-2'-one



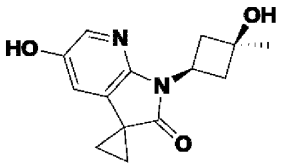
[1382] To a solution of 5'-bromo-1'-(3-oxocyclobutyl)-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-2'-one (700 mg, 2.28 mmol) in THF (11.4 mL) at 0 °C was added 3.0 M methyl magnesium bromide solution in THF (0.836 mL, 2.51 mmol) dropwise. The reaction was allowed to stir at 0 °C for 1 h, then was quenched with saturated aqueous NH_4Cl solution (30 mL), and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and then concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 50 g cartridge, 0–100% EtOAc/Hexanes) to provide 5'-bromo-1'-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-2'-one MS = 323.1 $[M+H]^+$.

Step 3: 1'-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-2'-one



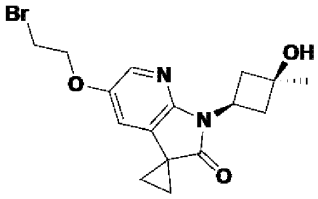
[1383] To a solution of 5'-bromo-1'-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-2'-one (480 mg, 1.49 mmol) and bis(pinacolato)diboron (0.566 g, 2.23 mmol) in 1,4-dioxane (4.95 mL) was added $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.121 g, 0.149 mmol) and KOAc (0.437 g, 4.46 mmol). The mixture was sparged with N_2 for 5 min, and then the reaction was heated at 90 °C for 16 h. The reaction was cooled to room temperature, diluted with EtOAc (20 mL), and filtered over Celite. The resulting filtrate was concentrated in vacuo to provide 1'-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-2'-one, which was used in the subsequent step without further purification. MS = 371.3 $[M+H]^+$.

Step 4: 5'-hydroxy-1'-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-2'-one



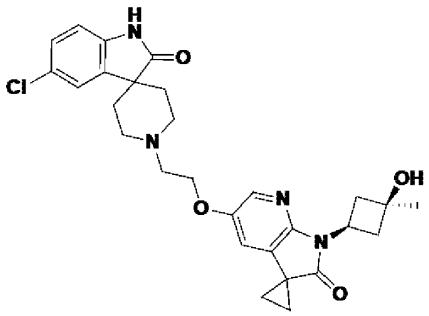
[1384] To a solution of 1'-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-5'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-2'-one (550 mg, 1.49 mmol) in MeOH (7.43 mL) was added 30% H_2O_2 in H_2O (0.486 mL, 4.46 mmol) dropwise. The reaction was stirred for 1 h, then was diluted with MeOH (20 mL) and concentrated in vacuo to provide 5'-hydroxy-1'-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-2'-one, which was used in the subsequent step without further purification. MS = 261.1 $[M+H]^+$.

Step 5: 5'-(2-bromoethoxy)-1'-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-2'-one



[1385] To a solution of 5'-hydroxy-1'-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-2'-one (400 mg, 1.54 mmol) in DMF (1.54 mL) was added 1,2-dibromoethane (7.68 mL) and Cs_2CO_3 (1.502 g, 4.61 mmol). The reaction was heated at 90 °C for 4 h, then was cooled to room temperature and diluted with EtOAc (30 mL). The solution was filtered over Celite and the filtrate was concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 25 g cartridge, 0–70% EtOAc/Hexanes) to provide 5'-(2-bromoethoxy)-1'-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-2'-one. MS = 367.13 $[M+H]^+$.

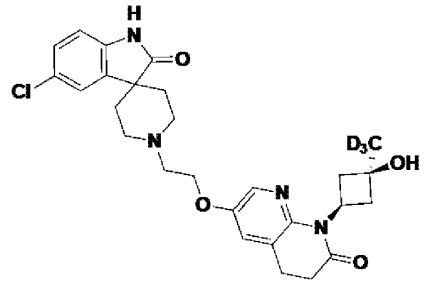
Step 6: 5-chloro-1'-(2-{2'-oxo-1'-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-5'-yloxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one



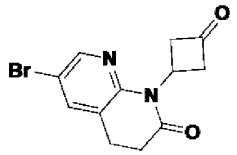
[1386] To a solution of 5'-(2-bromoethoxy)-1'-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-2'-one (100 mg, 0.272 mmol) and 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 74.0 mg, 0.272 mmol, HCl salt) in DMF (1.361 mL) was added K_2CO_3 (113 mg, 0.817 mmol) and KI (45.0 g, 0.272 mmol). The reaction was heated to 60 °C for 3 h. After cooling to room temperature, the mixture was diluted with H_2O (1.5 mL) and MeCN (0.5 mL), and then filtered. The filtrate was purified by reverse phase preparative HPLC (Phenomenex Kinetex C_{18} column, 5–50% MeCN in H_2O with 0.1% formic acid modifier) to give 5-chloro-1'-(2-{2'-oxo-1'-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-1',2'-dihydrospiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-5'-yloxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 460**). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.50 (s, 1H), 7.88 (d, J = 2.7 Hz, 1H), 7.50 (d, J = 2.2 Hz, 1H), 7.28 (d, J = 2.6 Hz, 1H), 7.24 (dd, J = 8.3, 2.1 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 5.13 (s, 1H), 4.48 – 4.38 (m, 1H), 4.16 (t, J = 5.7 Hz, 2H), 3.05 – 2.99 (m, 2H), 2.99 – 2.91 (m, 2H), 2.91 – 2.84 (m, 2H), 2.77 – 2.68 (m, 2H), 2.28 – 2.21 (m, 2H), 1.83 – 1.66 (m, 6H), 1.58 – 1.53 (m, 2H), 1.31 (s, 3H). MS = 523.17 $[M+H]^+$.

Example 94

5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-($^2H_3$)methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 461)

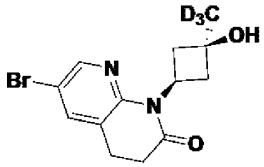


Step 1: 6-bromo-1-(3-oxocyclobutyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



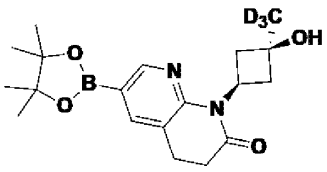
[1387] To a solution of 6-bromo-3,4-dihydro-1H-1,8-naphthyridin-2-one (5.00 g, 22.0 mmol) in DMF (100 mL) was added K_2CO_3 (9.13 g, 66.1 mmol). The mixture was stirred at 60 °C for 1 h, and then 3-bromocyclobutan-1-one (4.92 g, 33.0 mmol) was added dropwise via syringe pump over 20 h. The mixture was poured into H_2O (200 mL) and a solid precipitated. The solid was isolated via filtration, and the filter cake was dried in vacuo to provide 6-bromo-1-(3-oxocyclobutyl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one, which was used in the subsequent step without further purification. MS = 295.04 $[M+H]^+$.

Step 2: 6-bromo-1-[(*cis*)-3-hydroxy-3-($^2H_3$)methylcyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



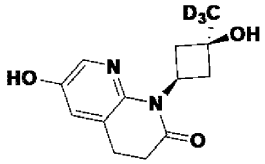
[1388] To a solution of 6-bromo-1-(3-oxocyclobutyl)-3,4-dihydro-1,8-naphthyridin-2-one (4.34 g, 14.7 mmol) in THF (73.5 mL) at 0 °C was added 1.0 M CD_3MgI in Et_2O (17.6 mL, 17.6 mmol) dropwise. The reaction was allowed to warm to room temperature and stirred for 1 h. The mixture was quenched with saturated aqueous NH_4Cl solution (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, then concentrated in vacuo. The residue was taken up in DCM, solids were removed by filtration, and the filtrate was concentrated in vacuo to give 6-bromo-1-[(*cis*)-3-hydroxy-3-($^2H_3$)methylcyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one. MS = 314.1 $[M+H]^+$.

Step 3: 1-[(*cis*)-3-hydroxy-3-($^2H_3$)methylcyclobutyl]-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



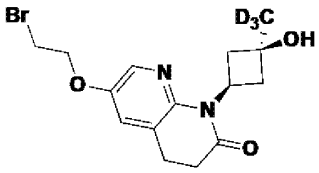
[1389] A solution of 6-bromo-1-[(*cis*)-3-hydroxy-3-($^2H_3$)methylcyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (4.13 g, 12.4 mmol), bis(pinacolato)diboron (4.71 g, 18.5 mmol), $Pd(dppf)Cl_2$ (0.904 g, 1.24 mmol), and KOAc (3.64 g, 37.1 mmol) in 1,4-dioxane (61.8 mL) was sparged with N_2, and then heated at 90 °C for 16 h. The reaction was cooled to room temperature and diluted with EtOAc (150 mL), then filtered over Celite. The resulting filtrate was concentrated in vacuo to give 1-[(*cis*)-3-hydroxy-3-($^2H_3$)methylcyclobutyl]-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one, which was used in the subsequent step without further purification. MS = 362.34 $[M+H]^+$.

Step 4: 6-hydroxy-1-[(*cis*)-3-hydroxy-3-($^2H_3$)methylcyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



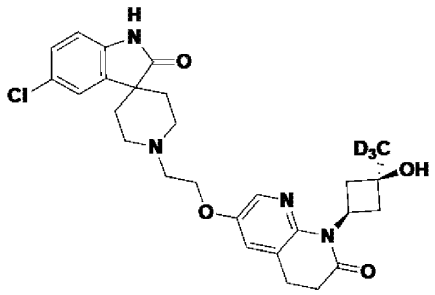
[1390] To a solution of 1-[(*cis*)-3-hydroxy-3-($^2H_3$)methylcyclobutyl]-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (4.46 g, 12.346 mmol) in MeOH (61.7 mL) was added 30% H_2O_2 in H_2O (3.78 mL, 37.0 mmol) dropwise. The reaction was allowed to stir at room temperature for 2 h, then was concentrated in vacuo to give 6-hydroxy-1-[(*cis*)-3-hydroxy-3-($^2H_3$)methylcyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one, which was used in the subsequent step without further purification. MS = 252.2 $[M+H]^+$.

Step 5: 6-(2-bromoethoxy)-1-[(*cis*)-3-hydroxy-3-($^2H_3$)methylcyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



[1391] 6-hydroxy-1-[(*cis*)-3-hydroxy-3-($^2H_3$)methylcyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (1.00 g, 3.98 mmol) was dissolved in DMF (3.98 mL), then Cs_2CO_3 (3.89 g, 11.9 mmol) and 1,2-dibromoethane (13.3 mL) were added and the reaction was heated at 90 °C for 8 h. The reaction was cooled to room temperature, filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 50 g cartridge, 0–100% EtOAc/Hexanes) to provide 6-(2-bromoethoxy)-1-[(*cis*)-3-hydroxy-3-($^2H_3$)methylcyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one. MS = 358.16 $[M+H]^+$.

Step 6: 5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-($^2H_3$)methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

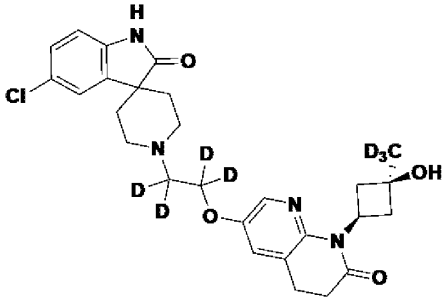


[1392] To a solution of 6-(2-bromoethoxy)-1-[(*cis*)-3-hydroxy-3-($^2H_3$)methylcyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one (500 mg, 1.40 mmol) and 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 0.381 g, 1.40 mmol, HCl salt) in DMF (2.79 mL) was added K_2CO_3 (0.579 g, 4.19 mmol) and KI (0.232 g, 1.40 mmol). The reaction was heated at 60 °C for 3 h. After cooling to room temperature, the reaction was poured over H_2O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were combined and washed with 5% LiCl solution in H_2O (50 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by reverse phase silica gel chromatography (Biotage 30 g C_{18} cartridge, 5–50% MeCN/H_2O with 0.1% NH_4OH) to give 5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-($^2H_3$)methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 461**). ^1H NMR (500 MHz, DMSO-d_6): δ 10.48 (s, 1H), 7.94 (d, J = 2.9 Hz, 1H), 7.50 (d, J = 2.2 Hz, 1H), 7.39 (d, J = 2.9 Hz, 1H), 7.23 (dd, J = 8.3, 2.1 Hz, 1H), 6.84 (d, J = 8.3 Hz, 1H), 4.81 (s, 1H), 4.28 – 4.20 (m, 1H), 4.18 (t, J = 5.7 Hz, 2H), 2.95 – 2.88 (m, 2H), 2.85 (t, J = 5.7 Hz, 2H), 2.82 – 2.77 (m,

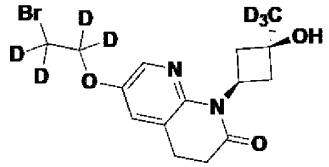
2H), 2.73 – 2.66 (m, 2H), 2.47 – 2.41 (m, 3H), 2.37 – 2.31 (m, 3H), 1.81 – 1.74 (m, 2H), 1.74 – 1.67 (m, 2H). MS = 514.27 $[M+H]^+$.

Example 95

5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-($^2H_3$)methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)(1,1,2,2-$^2H_4$)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 462)

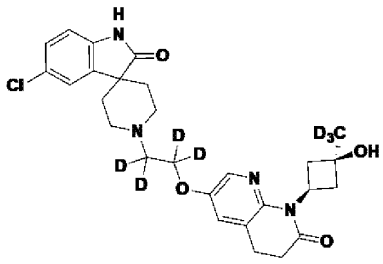


Step 1: 6-[2-bromo(1,1,2,2-$^2H_4$)ethoxy]-1-[(*cis*)-3-hydroxy-3-($^2H_3$)methylcyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one



[1393] To a solution of 6-hydroxy-1-[(*cis*)-3-hydroxy-3-($^2H_3$)methylcyclobutyl]-3,4-dihydro-1,8-naphthyridin-2-one (**Example 94,** Step 4, 3.00 g, 11.9 mmol) in DMF (23.9 mL) was added dibromo($^2H_4$)ethane (45.8 g, 239 mmol) and Cs_2CO_3 (11.7 g, 35.8 mmol). The reaction was heated at 90 °C for 8 h. The reaction was cooled to room temperature and diluted with EtOAc (100 mL), filtered through Celite, and the filtrate was concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 100 g cartridge, 0–80% EtOAc/Hexanes) to provide 6-[2-bromo(1,1,2,2-$^2H_4$)ethoxy]-1-[(*cis*)-3-hydroxy-3-($^2H_3$)methylcyclobutyl]-1,2,3,4-tetrahydro-1,8-naphthyridin-2-one. MS = 362.2 $[M+H]^+$.

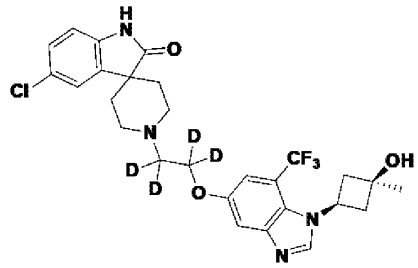
Step 2: 5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-($^2H_3$)methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)(1,1,2,2-$^2H_4$)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one



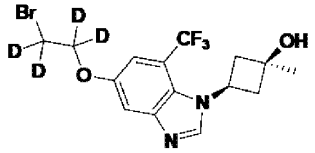
[1394] To a solution of 6-[2-bromo(1,1,2,2-$^2H_4$)ethoxy]-1-[(*cis*)-3-hydroxy-3-($^2H_3$)methylcyclobutyl]-3,4-dihydro-1,8-naphthyridin-2-one (1.40 g, 3.86 mmol) and 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 1.06 g, 3.86 mmol, HCl salt) in DMF (7.729 mL) was added K_2CO_3 (1.60 g, 11.6 mmol) and KI (0.642 g, 3.86 mmol). The reaction was heated at 60 °C for 3 h. The reaction was cooled to room temperature and diluted with EtOAc (50 mL). The mixture was then filtered through a pad of Celite, and the filtrate concentrated in vacuo. The crude product was purified by reverse phase silica gel chromatography (Biotage 30 g C_{18} cartridge, 5–50% MeCN/H_2O with 0.1% NH_4OH) to give 5-chloro-1'-[2-({7-oxo-8-[(*cis*)-3-hydroxy-3-($^2H_3$)methylcyclobutyl]-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl}oxy)(1,1,2,2-$^2H_4$)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one **(Compound 462)**. ^1H NMR (500 MHz, DMSO-d_6, 22/24 H): δ 10.43 (s, 1H), 7.87 (d, J = 2.9 Hz, 1H), 7.44 (d, J = 2.1 Hz, 1H), 7.32 (d, J = 2.9 Hz, 1H), 7.17 (dd, J = 8.2, 2.1 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 4.76 (s, 1H), 4.17 (p, J = 8.3 Hz, 1H), 2.92 – 2.79 (m, 2H), 2.73 (t, J = 7.2 Hz, 2H), 2.67 – 2.58 (m, 2H), 2.41 – 2.34 (m, 2H), 2.31 – 2.22 (m, 2H), 1.75 – 1.59 (m, 4H). MS = 518.3 $[M+H]^+$.

Example 97

5-chloro-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)(1,1,2,2-$^2H_4$)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 463)

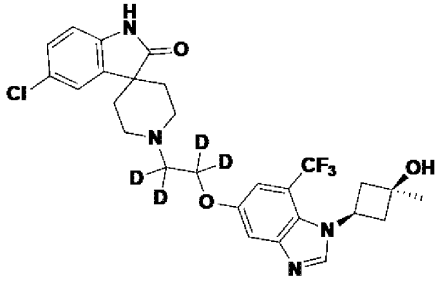


Step 1: (*cis*)-3-{5-[2-bromo(1,1,2,2-$^2H_4$)ethoxy]-7-(trifluoromethyl)-1,3-benzodiazol-1-yl}-1-methylcyclobutan-1-ol



[1395] To a solution of 1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-ol (**Intermediate A-92**, 250 mg, 0.873 mmol) and Cs_2CO_3 (0.854 g, 2.62 mmol) in DMF (1.747 mL) was added dibromo($^2H_4$)ethane (0.838 g, 4.367 mmol). The reaction was heated at 90 °C for 3 h. The reaction was cooled to room temperature and diluted with EtOAc (30 mL), and then filtered through a pad of Celite. The filtrate was concentrated, and the filtrate was purified by flash silica gel chromatography (Biotage 25 g cartridge, 0–10% MeOH/DCM) to provide (*cis*)-3-{5-[2-bromo(1,1,2,2-$^2H_4$)ethoxy]-7-(trifluoromethyl)-1,3-benzodiazol-1-yl}-1-methylcyclobutan-1-ol. MS = 397.2 / 399.2 $[M+H]^+$.

Step 2: 5-chloro-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)(1,1,2,2-$^2H_4$)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one

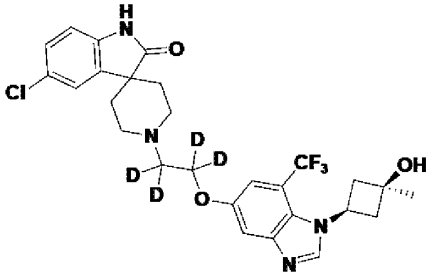


[1396] To a solution of (*cis*)-3-{5-[2-bromo(1,1,2,2-$^2H_4$)ethoxy]-7-(trifluoromethyl)-1,3-benzodiazol-1-yl}-1-methylcyclobutan-1-ol (257 mg, 0.647 mmol) and 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 0.177 g, 0.647 mmol, HCl salt) in DMF (1.29 mL) was added K_2CO_3 (0.268 g, 1.94 mmol) and KI (0.107 g, 0.647 mmol). The reaction was heated at 60 °C for 3 h, then was cooled to room temperature and the solution was diluted with H_2O 1.5 mL) and MeCN 1.5 mL). The mixture was purified by reverse phase silica gel chromatography (Biotage 30 g C_{18} cartridge, 5–60% MeCN/H_2O with 0.1% NH_4OH) to give 5-chloro-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-

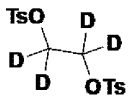
yl}oxy)(1,1,2,2-$^2H_4$)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 463**). ^1H NMR (500 MHz, DMSO-d_6): δ 10.42 (s, 1H), 8.61 (s, 1H), 7.54 (d, J = 2.4 Hz, 1H), 7.43 (d, J = 2.1 Hz, 1H), 7.19 (d, J = 2.4 Hz, 1H), 7.16 (dd, J = 8.2, 2.1 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 5.25 (s, 1H), 4.51 (p, J = 8.3 Hz, 1H), 2.92 – 2.83 (m, 2H), 2.70 – 2.60 (m, 2H), 2.59 – 2.48 (m, 4H), 1.78 – 1.69 (m, 2H), 1.68 – 1.59 (m, 2H), 1.27 (s, 3H). MS = 553.2 $[M+H]^+$.

Alternative Procedure for Example 97

5-chloro-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)(1,1,2,2-$^2H_4$)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 463)

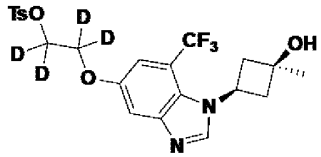


Step 1: 1-methyl-4-({2-[(4-methylbenzenesulfonyl)oxy](1,1,2,2-$^2H_4$)ethoxy}sulfonyl)benzene



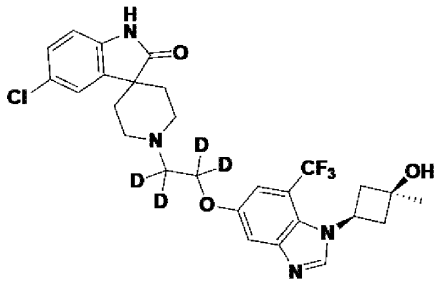
[1397] To a 0 °C mixture of ($^2H_4$)ethane-1,2-diol (5.00 g, 75.7 mmol) and TsCl (31.7 g, 166 mmol) in DCM (150 mL) was added dropwise TEA (26.3 mL, 189 mmol). The mixture was stirred at room temperature for 16 h. The mixture was poured into ice water (300 mL) and extracted with DCM (2 x 100 mL). The combined organic layers were washed with 10% w/w citric acid in H_2O (200 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was triturated in MTBE (150 mL) for 30 min. The mixture was filtered to collect the solid, which was dried in vacuo to provide 1-methyl-4-({2-[(4-methylbenzenesulfonyl)oxy](1,1,2,2-$^2H_4$)ethoxy}sulfonyl)benzene, which was used in the subsequent step without further purification. MS = 374.9 $[M+H]^+$.

Step 2: 2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)(1,1,2,2-$^2H_4$)ethyl 4-methylbenzene-1-sulfonate



[1398] A mixture of 1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-ol (**Intermediate A-92**, 1.00 g, 3.49 mmol), 1-methyl-4-({2-[(4-methylbenzenesulfonyl)oxy](1,1,2,2-$^2H_4$)ethoxy}sulfonyl)benzene (3.92 g, 10.5 mmol) and K_2CO_3 (1.45 g, 10.5 mmol) in DMF (60 mL) was stirred at 50 °C for 16 h. After cooling to room temperature, the mixture was poured into H_2O (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Sepaflash 20 g cartridge, 0–80% EtOAc/Petroleum ether) to provide 2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)(1,1,2,2-$^2H_4$)ethyl 4-methylbenzene-1-sulfonate. MS = 489.1 $[M+H]^+$.

Step 3: 5-chloro-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)(1,1,2,2-$^2H_4$)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 463)

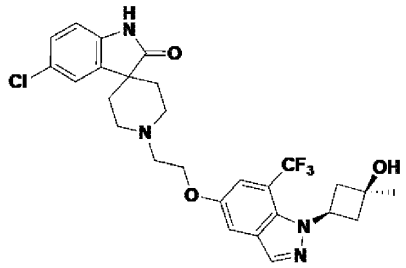


[1399] A mixture of 2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)(1,1,2,2-$^2H_4$)ethyl 4-methylbenzene-1-sulfonate (700 mg, 1.43 mmol), 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 431 mg, 1.58 mmol, HCl salt) and $NaHCO_3$ (602 mg, 7.16 mmol) in MeCN (30 mL) was stirred at 80 °C for 16 h. After cooling to room temperature, solids precipitated out. The solids were isolated by filtration, and the filter cake was further purified by reverse phase preparative HPLC (Phenomenex Luna C_{18} column, 5–50% MeCN:0.04% HCl in H_2O) to give 5-chloro-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-

7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)(1,1,2,2-$^2H_4$)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 463, HCl salt, 24/24 H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.09 (br s, 0.5H), 10.81 (s, 0.5H), 10.73 (s, 0.5H), 10.49 (br s, 0.5H), 9.08 – 9.03 (m, 1H), 7.99 (s, 0.5H), 7.73 – 7.71 (m, 1H), 7.50 – 7.40 (m, 1H), 7.26 – 7.24 (m, 1H), 7.17 (s, 0.5H), 6.94 – 6.88 (m, 1H), 4.64 – 4.55 (m, 1H), 3.88 – 3.59 (m, 4H), 2.67 – 2.50 (m, 5H), 2.21 – 1.97 (m, 1H), 1.98 – 1.95 (m, 2H), 1.34 (s, 3H). MS = 552.9 $[M+H]^+$.

Example 98

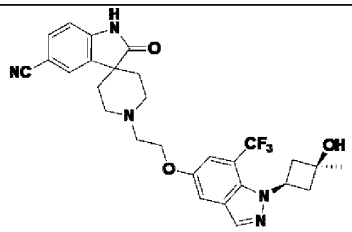
5-chloro-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-indazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 464)



[1400] A mixture of 2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-indazol-5-yl}oxy)ethyl 4-methylbenzene-1-sulfonate (**Intermediate A-123**, 80.0 mg, 165 μmol), 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 49.6 mg, 182 μmol, HCl salt) and $NaHCO_3$ (69.4 mg, 826 μmol) in MeCN (4 mL) was stirred at 80 °C for 16 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure. The filtrate was purified by reverse phase preparative HPLC (Phenomenex Luna C_{18} column, 5–35% MeCN:0.04% HCl in H_2O) to give 5-chloro-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-indazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 464**). ^{1}H NMR (400 MHz, DMSO-d_6, HCl salt): δ 10.80 (s, 0.5H), 10.73 (s, 0.5H), 10.60 (br s, 0.5H), 10.09 (s, 0.5H), 8.34 (d, J = 2.8 Hz, 1H), 7.99 (s, 0.5H), 7.74 (s, 1H), 7.58 (dd, J = 12.0 Hz, 2.0 Hz, 1H), 7.35 – 7.25 (m, 1H), 7.16 (d, J = 1.6 Hz, 0.5H), 6.94 – 6.88 (m, 1H), 5.29 (br s, 1H), 4.80 – 4.73 (m, 1H), 4.54 – 4.53 (m, 2H), 3.90 – 3.75 (m, 5H), 3.45 – 3.35 (m, 1H), 2.76 (t, J = 10.8 Hz, 2H), 2.50 – 2.45 (m, 3H), 2.24 – 2.12 (m, 1H), 2.06 – 1.86 (m, 2H), 1.16 (s, 3H). MS = 549.2 $[M+H]^+$.

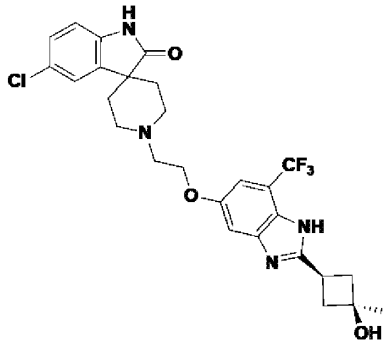
[1401] The following compounds in **Table 38.20** were prepared according to procedures similar to steps described for **Example 98** using the appropriate starting materials or common intermediates.

Table 38.20

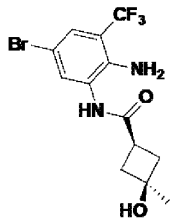
#	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Inter-mediates Used
465		2-oxo-1'-[2-({1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-indazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 540.2 Found 540.2	**A-123** & **B-9**

Example 99

5-chloro-1'-[2-({2-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 466)

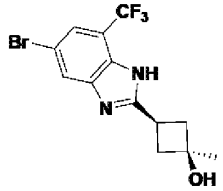


Step 1: (*cis*)-*N*-[2-amino-5-bromo-3-(trifluoromethyl)phenyl]-3-hydroxy-3-methylcyclobutane-1-carboxamide



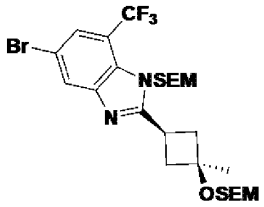
[1402] To a solution of 3-hydroxy-3-methyl-cyclobutanecarboxylic acid (1.53 g, 11.8 mmol) in DCM (30 mL) was added DIEA (5.12 mL, 29.4 mmol) and HATU (5.37 g, 14.1 mmol). After stirring at room temperature for 20 min, 5-bromo-3-(trifluoromethyl)benzene-1,2-diamine (3.00 g, 11.76 mmol) was added. The mixture was stirred at room temperature for 2 h, then was poured into H_2O (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give (*cis*)-*N*-[2-amino-5-bromo-3-(trifluoromethyl)phenyl]-3-hydroxy-3-methylcyclobutane-1-carboxamide. MS = 367.0 / 369.0 $[M+H]^+$.

Step 2: (*cis*)-3-[5-bromo-7-(trifluoromethyl)-1H-1,3-benzodiazol-2-yl]-1-methylcyclobutan-1-ol



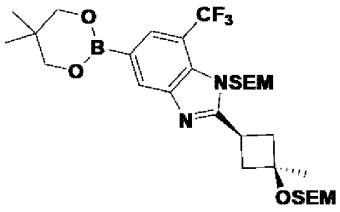
[1403] A solution of (*cis*)-*N*-[2-amino-5-bromo-3-(trifluoromethyl)phenyl]-3-hydroxy-3-methylcyclobutane-1-carboxamide (5.00 g, 13.6 mmol) in acetic acid (50 mL) was heated to 90 °C and stirred at 90 °C for 5 h. After cooling to 0 °C, the reaction mixture was adjusted to pH = 7 by addition of saturated aqueous Na_2CO_3 solution, then was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Sepaflash 40 g cartridge, 0–60% EtOAc/Petroleum ether) to provide (*cis*)-3-[5-bromo-7-(trifluoromethyl)-1H-1,3-benzodiazol-2-yl]-1-methylcyclobutan-1-ol. MS =349.0 / 350.9 $[M+H]^+$.

Step 3: 5-bromo-2-[(*cis*)-3-methyl-3-{[2-(trimethylsilyl)ethoxy]methoxy}cyclobutyl]-7-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,3-benzodiazole



[1404] To a 0 °C solution of (*cis*)-3-[5-bromo-7-(trifluoromethyl)-1H-1,3-benzodiazol-2-yl]-1-methylcyclobutan-1-ol (1.50 g, 4.30 mmol) in THF (20 mL) was added NaH (309 mg, 7.73 mmol, 60% in mineral oil) portion wise. The mixture was stirred at 0 °C for 30 min, and then a solution of SEMCl (1.52 mL, 8.59 mmol) in THF (8 mL) was added dropwise. The resulting mixture was warmed to room temperature and then stirred for 16 h. The reaction was cooled to 0–10 °C, quenched with saturated aqueous NH_4Cl solution (20 mL), and then extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by reverse phase preparative HPLC (Welch Xtimate C_{18} column, 45–65% MeCN:10 mM NH_4HCO_3 in H_2O) to give 5-bromo-2-[(*cis*)-3-methyl-3-{[2-(trimethylsilyl)ethoxy]methoxy}cyclobutyl]-7-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,3-benzodiazole. MS =609.0 / 611.0 $[M+H]^+$

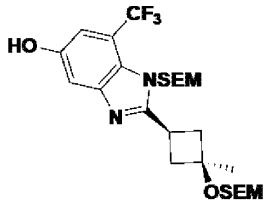
Step 4: 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-2-[(*cis*)-3-methyl-3-{[2-(trimethylsilyl)ethoxy]methoxy}cyclobutyl]-7-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,3-benzodiazole



[1405] A mixture of 5-bromo-2-[(*cis*)-3-methyl-3-{[2-(trimethylsilyl)ethoxy]methoxy}cyclobutyl]-7-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,3-benzodiazole (300 mg, 492 μmol), KOAc (72.4 mg, 738 μmol), $Pd(dppf)Cl_2$ (18.0 mg, 24.6 μmol), and bis(neopentyl glycolato)diboron (222 mg, 984 μmol) in 1,4-dioxane (5 mL) was degassed and purged with N_2 (3x), and then the mixture was heated to 90 °C and stirred at 90 °C for 3 h under N_2 atmosphere. After cooling to room temperature, the reaction mixture was filtered, and the filtrate was concentrated in vacuo to give 5-(5,5-dimethyl-1,3,2-

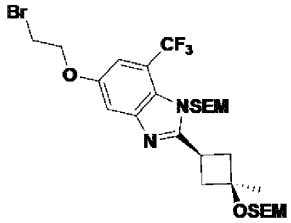
dioxaborinan-2-yl)-2-[(*cis*)-3-methyl-3-{[2-(trimethylsilyl)ethoxy]methoxy}cyclobutyl]-7-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,3-benzodiazole, which was used in the subsequent step without further purification. MS =575.3 $[M-C_5H_8+H]^+$

Step 5: 2-[(*cis*)-3-methyl-3-{[2-(trimethylsilyl)ethoxy]methoxy}cyclobutyl]-7-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,3-benzodiazol-5-ol



[1406] To a solution of 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-2-[(*cis*)-3-methyl-3-{[2-(trimethylsilyl)ethoxy]methoxy}cyclobutyl]-7-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,3-benzodiazole (600 mg, 934 μmol) in THF (6 mL) and H_2O (2 mL) was added Oxone (861 mg, 1.40 mmol). The mixture was stirred at room temperature for 2 h, then was quenched with saturated aqueous Na_2SO_3 solution (30 mL), and extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Biotage 12 g cartridge, 0–19% EtOAc/Petroleum ether) to provide 2-[(*cis*)-3-methyl-3-{[2-(trimethylsilyl)ethoxy]methoxy}cyclobutyl]-7-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,3-benzodiazol-5-ol. MS = 547.2 $[M+H]^+$.

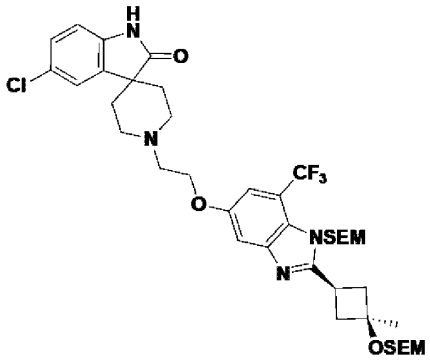
Step 6: 5-(2-bromoethoxy)-2-[(*cis*)-3-methyl-3-{[2-(trimethylsilyl)ethoxy]methoxy}cyclobutyl]-7-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,3-benzodiazole



[1407] To a solution of 2-[(*cis*)-3-methyl-3-{[2-(trimethylsilyl)ethoxy]methoxy}cyclobutyl]-7-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,3-benzodiazol-5-ol (130 mg, 238 μmol) and 1,2-dibromoethane (206 μL, 2.38 mmol) in *i*-PrOH (5 mL) was added Cs_2CO_3 (232 mg,

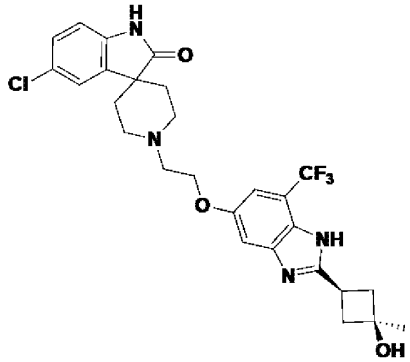
713 μmol). The mixture was heated to 60 °C and stirred at 60 °C for 12 h. After cooling to room temperature, the reaction mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash silica gel chromatography (Sepaflash 4 g cartridge, 0–15% EtOAc/Petroleum ether) to provide 5-(2-bromoethoxy)-2-[(*cis*)-3-methyl-3-{[2-(trimethylsilyl)ethoxy]methoxy}cyclobutyl]-7-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,3-benzodiazole. MS =653.1 / 655.1 $[M+H]^+$

Step 7: 5-chloro-1'-[2-({2-[(*cis*)-3-methyl-3-{[2-(trimethylsilyl)ethoxy]methoxy}cyclobutyl]-7-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one



[1408] To a solution of 5-(2-bromoethoxy)-2-[(*cis*)-3-methyl-3-{[2-(trimethylsilyl)ethoxy]methoxy}cyclobutyl]-7-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,3-benzodiazole (60.0 mg, 91.78 μmol) and 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 30.1 mg, 110 μmol, HCl salt) in MeCN (3 mL) was added $NaHCO_3$ (38.6 mg, 459 μmol). The mixture was heated to 80 °C and stirred at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated in vacuo to give 5-chloro-1'-[2-({2-[(*cis*)-3-methyl-3-{[2-(trimethylsilyl)ethoxy]methoxy}cyclobutyl]-7-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one, which was used in the subsequent step without further purification. MS = 809.3 $[M+H]^+$.

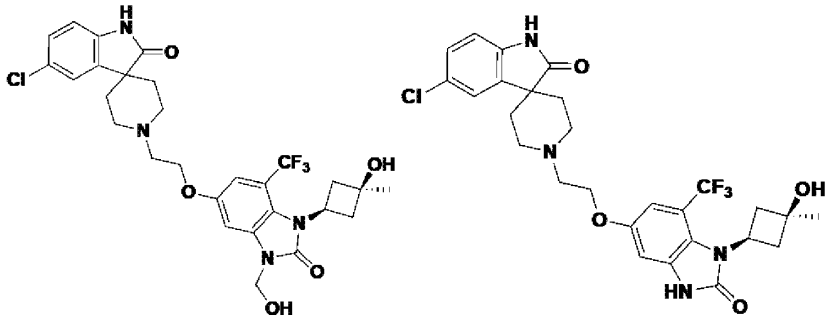
Step 8: 5-chloro-1'-[2-({2-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 466)



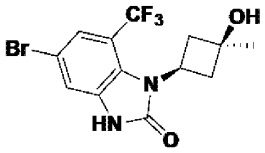
[1409] To a mixture of 5-chloro-1'-[2-({2-[(*cis*)-3-methyl-3-{[2-(trimethylsilyl)ethoxy]methoxy}cyclobutyl]-7-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (90.0 mg, 111 μmol) in DCM (2 mL) was added TFA (165 μL, 2.22 mmol). The mixture was stirred at room temperature for 16 h, and then DCM was removed under reduced pressure. The residue was dissolved in THF (2 mL) and then 30% $NH_3 \cdot H_2O$ in H_2O (285 μL, 2.22 mmol) was added. The mixture was stirred at room temperature for 1 h, then was concentrated under reduced pressure to remove THF. The residual mixture was purified by reverse phase preparative HPLC (Waters Xbridge BEH C_{18} column, 30–60% MeCN:10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-[2-({2-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 466**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.43 (br s, 1H), 10.49 (s, 1H), 7.50 (s, 1H), 7.29 – 7.20 (m, 2H), 7.06 (s, 1H), 6.84 (d, J = 8.4 Hz, 1H), 5.15 (br s, 1H), 4.21 (t, J = 5.6 Hz, 2H), 3.32 – 3.20 (m, 1H), 2.90 – 2.85 (m, 4H), 2.73 – 2.68 (m, 2H), 2.40 – 2.30 (m, 4H), 1.80 – 1.70 (m, 4H), 1.19 (s, 3H). MS = 549.1 $[M+H]^+$.

Example 100

5-chloro-1'-(2-{[3-(hydroxymethyl)-2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2,3-dihydro-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 467) and 5-chloro-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2,3-dihydro-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 468)

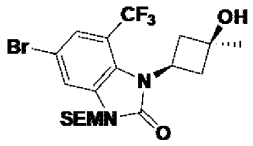


Step 1: 5-bromo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2,3-dihydro-1H-1,3-benzodiazol-2-one



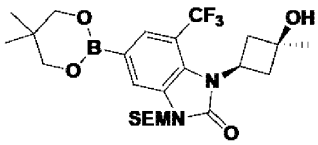
[1410] A solution of (*cis*)-3-{[2-amino-4-bromo-6-(trifluoromethyl)phenyl]amino}-1-methylcyclobutan-1-ol (General procedure for **Intermediate A-92**, Step 3, 2.00 g, 5.90 mmol) and carbonyl diimidazole (1.43 g, 8.85 mmol) in THF (20 mL) was warmed to 50 °C and stirred at 50 °C for 16 h. After cooling to room temperature, the reaction mixture was poured into H_2O (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were concentrated in vacuo. The residue was dissolved into THF (30 mL) and H_2O (10 mL) and LiOH•H_2O (1.01 g, 24.2 mmol) was added. The mixture was stirred at 50 °C for 2 h. After cooling to room temperature, the reaction mixture was poured into H_2O (100 mL) and extracted with EtOAc (2 x 200 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo give 5-bromo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2,3-dihydro-1H-1,3-benzodiazol-2-one, which was used in the subsequent step without further purification. MS = 365.0 / 367.0 $[M+H]^+$.

Step 2: 6-bromo-3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-4-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-1,3-benzodiazol-2-one



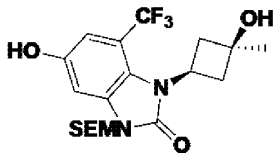
[1411] To a 0 °C mixture of 5-bromo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2,3-dihydro-1H-1,3-benzodiazol-2-one (2.70 g, 7.39 mmol) in THF (30 mL) was added NaH (887 mg, 22.2 mmol, 60% in mineral oil) portion wise. (2-(chloromethoxy)ethyl)trimethylsilane (2.62 mL, 14.8 mmol) was added dropwise to the 0 °C reaction mixture. The mixture was stirred at 0 °C for 2 h, then was quenched with ice water (30 mL). After stirring at 0 °C for an additional 10 min, the mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Sepaflash 20 g cartridge, 0–60% EtOAc/Petroleum ether) to provide 6-bromo-3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-4-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-1,3-benzodiazol-2-one. MS = 495.0 / 497.0 $[M+H]^+$.

Step 3: 6-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-4-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-1,3-benzodiazol-2-one



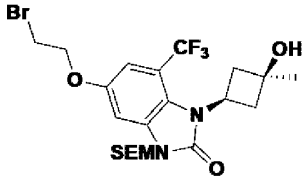
[1412] A mixture of 6-bromo-3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-4-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-1,3-benzodiazol-2-one (1.20 g, 2.42 mmol), $Pd(dppf)Cl_2$ (88.6 mg, 121 μmol), KOAc (357 mg, 3.63 mmol) and bis(neopentyl glycolato)diboron (1.09 g, 4.84 mmol) in 1,4-dioxane (15 mL) was degassed and purged with N_2 (3x), and then the mixture was stirred at 90 °C for 3 h under N_2 atmosphere. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give 6-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-4-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-1,3-benzodiazol-2-one, which was used in the subsequent step without further purification. MS = 461.2 $[M–C_5H_8+H]^+$.

Step 4: 6-hydroxy-3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-4-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-1,3-benzodiazol-2-one



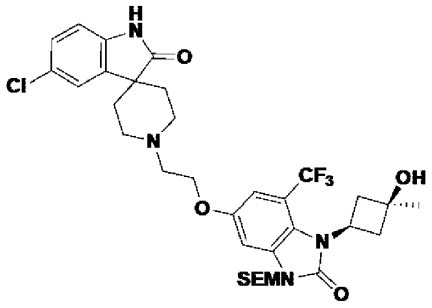
[1413] To a solution of 6-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-4-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-1,3-benzodiazol-2-one (2.30 g, 4.35 mmol) in THF (16 mL) and H_2O (8 mL) was added Oxone (4.01 g, 6.53 mmol). The mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with saturated aqueous Na_2SO_3 solution (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 6-hydroxy-3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-4-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-1,3-benzodiazol-2-one, which was used in the subsequent step without further purification. MS = 433.2 $[M+H]^+$.

Step 5: 6-(2-bromoethoxy)-3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-4-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-1,3-benzodiazol-2-one



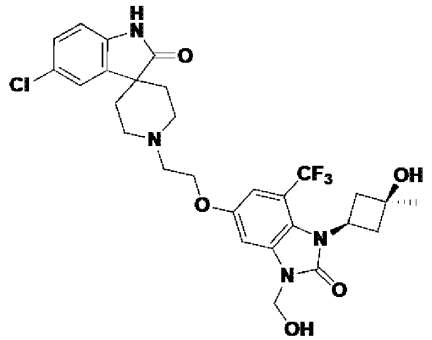
[1414] To a solution of 6-hydroxy-3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-4-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-1,3-benzodiazol-2-one (1.60 g, 3.70 mmol) and 1,2-dibromoethane (2.79 mL, 37.0 mmol) in *i*-PrOH (20 mL) was added Cs_2CO_3 (3.62 g, 11.1 mmol). The mixture was stirred at 60 °C for 12 h. After cooling to room temperature, the reaction mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash silica gel chromatography (Sepaflash 20 g cartridge, 0–18% EtOAc/Petroleum ether) to provide 6-(2-bromoethoxy)-3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-4-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-1,3-benzodiazol-2-one. MS = 539.1 / 541.0 $[M+H]^+$.

Step 6: 5-chloro-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-3-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one



[1415] To a solution of 6-(2-bromoethoxy)-3-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-4-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-1,3-benzodiazol-2-one (100 mg, 185 μmol) and 5-chloro-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Intermediate B-4**, 50.6 mg, 185 μmol, *HCl salt*) in MeCN (5 mL) was added $NaHCO_3$ (77.9 mg, 927 μmol). The mixture was warmed to 80 °C and stirred at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was filtered, and the filtrate was concentrated in vacuo to give 5-chloro-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-3-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one, which was used in the subsequent step without further purification. MS = 695.2 $[M+H]^+$.

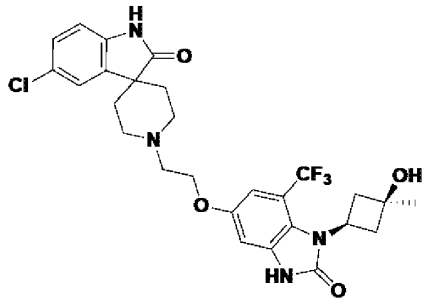
Step 7: 5-chloro-1'-(2-{[3-(hydroxymethyl)-2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2,3-dihydro-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 467)



[1416] To a mixture of 5-chloro-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-3-{[2-(trimethylsilyl)ethoxy]methyl}-2,3-dihydro-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (70.0 mg, 101 μmol) in DCM (1 mL) was added TFA (74.8 μL, 1.01 mmol). The mixture was stirred at room temperature for 1 h, then

concentrated in vacuo. The residue was purified by reverse phase preparative HPLC (Phenomenex Luna OBD C_{18} column, 5–35% MeCN:0.04% HCl in H_2O) to give 5-chloro-1'-(2-{[3-(hydroxymethyl)-2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2,3-dihydro-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (**Compound 467,** HCl salt). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.82 (s, 0.5H), 10.74 (s, 0.5H), 10.41 (br s, 0.5H), 10.02 (br s, 0.5H), 8.00 (s, 0.5H), 7.40 (s, 1H), 7.38 – 7.30 (m, 1H), 7.16 (s, 0.5H), 7.06 (s, 1H), 6.94 – 6.90 (m, 1H), 6.62 – 6.50 (m, 1H), 5.28 (d, J = 5.6 Hz, 2H), 5.27 – 5.15 (m, 1H), 4.52 – 4.50 (m, 2H), 4.30 – 4.25 (m, 1H), 3.95 – 3.50 (m, 6H), 3.21 (d, J = 9.2 Hz, 2H), 2.50 – 2.40 (m, 1H), 2.20 – 2.17 (m, 3H), 2.18 – 1.90 (m, 2H), 1.23 (s, 3H). MS = 595.1 $[M+H]^+$.

Step 8: 5-chloro-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2,3-dihydro-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (Compound 468)

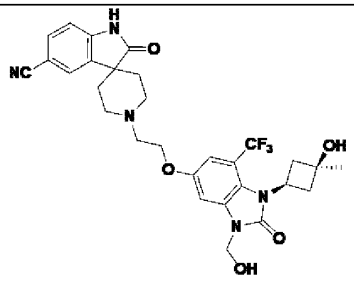
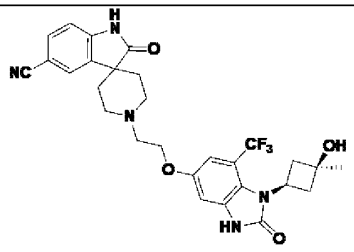


[1417] To a solution of 5-chloro-1'-(2-{[3-(hydroxymethyl)-2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2,3-dihydro-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one (170 mg, 286 μmol) in THF (2 mL) was added 30% NH_3•H_2O in H_2O (4.00 mL, 31.2 mmol). The mixture was stirred at room temperature for 2 h, then was concentrated in vacuo. The residue was purified by reverse phase preparative HPLC (Waters Xbridge OBD C_{18} column, 20–55% MeCN:10 mM NH_4HCO_3 in H_2O) to give 5-chloro-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2,3-dihydro-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidin]-2-one **(Compound 468)**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.38 (s, 1H), 10.49 (s, 1H), 7.48 (d, J = 2.0 Hz, 1H), 7.25 – 7.20 (m, 1H), 6.88 (s, 2H), 6.84 (d, J = 8.0 Hz, 1H), 5.13 (s, 1H), 4.25 – 4.15 (m, 3H), 3.21 (t, J = 9.2 Hz, 2H), 2.93 – 2.82

(m, 4H), 2.71 – 2.67 (m, 2H), 2.20 – 2.18 (m, 2H), 1.81 – 1.66 (m, 4H), 1.27 (s, 3H). MS = 565.2 $[M+H]^+$.

[1418] The following compounds in **Table 38.21** were prepared according to procedures similar to steps described for **Example 100** using the appropriate starting materials or common intermediates.

Table 38.21

#	Structure	IUPAC Name	Exact Mass $[M+H]^+$	Inter-mediates Used
469		1'-(2-{[3-(hydroxymethyl)-2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2,3-dihydro-1H-1,3-benzodiazol-5-yl]oxy}ethyl)-2-oxo-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 586.2 Found 586.1	**B-9**
470		2-oxo-1'-[2-({2-oxo-1-[(*cis*)-3-hydroxy-3-methylcyclobutyl]-7-(trifluoromethyl)-2,3-dihydro-1H-1,3-benzodiazol-5-yl}oxy)ethyl]-1,2-dihydrospiro[indole-3,4'-piperidine]-5-carbonitrile	Calc'd 556.2 Found 556.2	**B-9**

Biological Examples

Example B1

[1419] This example shows that compounds of the present disclosure are able to inhibit calcium transport by APOL1.

[1420] A HEK293 clonal cell line was generated to stably express GCaMP6f, a genetically encoded calcium indicator, and inducibly express APOL1 G2 (HEK T-REx/GCaMP6f/APOL1 G2 K6.3). Cells were maintained in the following standard complete medium: DMEM with 4.5 g/L glucose and sodium pyruvate (BioWhittaker, Lonza, BE12-614F), supplemented with 10% FBS Performance Plus (Gibco, 16000044), 1% penicillin-streptomycin (BioWhittaker, DE17-602E), 2 mM ultraglutamine-1 (BioWhittaker cat. BE 17-605/U1), 50 µg/mL Zeocin (InvivoGen, ant-zn), 2.5 µg/mL Blasticidin (InvivoGen, ant-bl-5), and 25 µg/mL Hygromycin (InvivoGen, ant-hg). Standard propagation conditions consisted of plating $9x10^6$, $4x10^6$, $2x10^6$ cells in a T225 flasks to be processed after 2, 3, or 4 days, respectively.

[1421] A source plate was generated containing 20 serially diluted compounds in DMSO (duplicate 8-point dose response). Next, 0.8 µL of compounds were transferred from the source plate to a destination plate prefilled with 79.2 µL of Ca^{2+} free Tyrode's buffer (130 mM NaCl, 5 mM KCl, 1 mM $MgCl_2$, 5 mM $NaHCO_3$, 20 mM HEPES at pH 7.4). The destination plate was placed on a plate shaker (5 seconds at 2000 rpm) to mix. This process resulted in a destination plate with 2X concentrated compound solutions. All transfer and mixing steps were conducted with an CyBi®-Well dispenser.

[1422] Cells were split by gently washing with DPBS (Euroclone, ECB4004L), followed by a 5-minute incubation (humidified, 37˚C with 5% CO_2) with trypsin-EDTA solution (Euroclone, ECB3052D). Detached cells were diluted with standard complete medium without selective agents, counted, and plated in a 384 MTP microplate (GR4332CPL, Twin Helix) (10,000 cells/well in 25 µl/well) using a MATRIX WellMate dispenser. Plates were placed into a humidified incubator (37°C with 5% CO_2) overnight. The following day, 20 µL of doxycycline (Sigma, D9891) at 20 ng/mL in standard complete medium was added to cells with a CyBi ®Drop dispenser to induce APOL1 G2 expression. After a 6-hour incubation (humidified, 37˚C with 5% CO_2), cells were washed 3 times with Ca^{2+} free Tyrode's Buffer (130 mM NaCl, 5 mM KCl, 1 mM $MgCl_2$, 5 mM $NaHCO_3$, 20 mM HEPES at pH 7.4) using a BIOTEK Microplate washer, such that 10 µL of buffer remained in each well after the final wash. Assay plates were then stored at room temperature for 10 minutes. Next, 10µL of diluted compounds were transferred to the assay plate from the 2X compound plate using a CyBi®-Well dispenser. Compound incubation was then carried out at room

temperature for 10 minutes. The assay plate was transferred to the FLIPR^{TETRA} and 20 µL of 10 mM Ca^{2+} (final concentration = 5 mM) Tyrode's buffer was injected.

[1423] Table 39 below summarizes the data from this experiment. Unless otherwise specified, AC_{50} and values are reported as the geometric mean of at least 2 assay runs on separate days. Each run represents the average of a technical replicate, where each compound was assayed twice in the same plate. A superscript † symbol indicates a value from the average of a technical replicate from a single assay run, where each compound was assayed twice in the same plate.

[1424] The AC_{50} values in Table 39 below reflect the compound's ability to prevent calcium influx by inhibiting APOL1. As shown in the table, numerous compounds of the present disclosure are able to potently inhibit APOL1-mediated calcium transport at sub micromolar concentrations. Compounds in Table 39 are referred to by the corresponding Compound Number in Table 1, which is also referred to in the synthetic examples. When one or more of the numbered compounds are identified by stereochemistry (for example, (*R*)- or (*S*)-), the specific stereoisomer for which data is provided in Table 39 may be identified by the elution order of such compound as described in the synthetic examples. For example, Compounds 39 and 40 are associated with Step 5 of Example 13, where **Compound 39** is the first eluting enantiomer, and **Compound 40** is the second eluting enantiomer in the chiral separation of **Compound 38**. For Table 39 below, n/a represents "not available".

Table 39.

Cmpd No.	APOL1 G2 FLIPR AC_{50} (µM)	Cmpd No.	APOL1 G2 FLIPR AC_{50} (µM)	Cmpd No.	APOL1 G2 FLIPR AC_{50} (µM)
1	0.703	17	1.10	29	0.586†
4	0.670	18	0.240	30	0.409†
7	0.601	19	0.481	31	0.37†
8	0.833	20	0.348	32	0.262
9	1.31	21	< 0.213	33	0.218
10	1.27	22	0.306	34	0.168
11	1.05†	23	0.514	35	0.142
12	< 0.457	24	0.2	36	0.223
13	< 0.587	25	0.651†	37	0.327
14	0.704	26	0.943	38	0.307
15	0.654	27	0.51	39	0.745
16	1.16	28	< 0.434	40	0.657

Cmpd No.	APOL1 G2 FLIPR AC_{50} (μM)
41	0.709
42	0.316
43	0.507
44	0.352
45	0.746
46	0.434
47	0.641
48	0.567
49	0.875†
50	0.622
51	0.953†
52	0.615†
53	0.838
54	0.804
55	< 0.284
56	1.01
57	0.706
58	< 0.320
59	0.879
60	0.652
61	0.686
62	0.958
63	0.461
64	0.455
65	0.639
66	0.461
67	0.351
68	< 0.249
69	0.216
70	0.124
71	0.626
72	0.252
73	0.161
74	0.781
75	0.689
76	0.678
77	1.60†
78	0.522
79	0.687
80	0.375

Cmpd No.	APOL1 G2 FLIPR AC_{50} (μM)
81	0.549†
82	1.05†
83	0.718
84	1.45†
85	0.564
86	0.539
87	0.375
88	0.698
89	0.463
90	0.973
91	0.739
92	0.761
93	0.951
94	0.794
95	0.655†
96	0.552
97	0.823
98	0.6
99	0.643
100	0.503
101	0.634
102	0.671
103	0.591
104	0.408
105	0.392
106	0.756
107	0.712
108	0.86
109	1.19
110	0.772
111	0.919
112	0.746
113	0.524
114	0.529
115	0.472†
116	0.466†
117	0.396†
118	1.04†
119	1.01†
120	1.19†

Cmpd No.	APOL1 G2 FLIPR AC_{50} (μM)
121	0.508
122	0.616
123	0.796
124	0.727
125	0.729†
126	0.624†
127	0.542†
128	0.537†
129	0.352
130	0.525
131	0.464
132	0.492†
133	0.671†
134	0.879†
135	0.763†
136	0.80†
137	0.597†
138	1.22†
139	1.12†
140	0.807†
141	0.954†
142	0.845
143	0.701
144	0.708†
145	0.465†
146	0.279†
147	0.492
148	0.96
149	0.971
150	0.629
151	1.74
152	1.82
153	0.826†
154	0.869†
155	0.452†
156	0.468†
157	0.933†
158	0.845†
159	1.01†
160	0.898

Cmpd No.	APOL1 G2 FLIPR AC_{50} (μM)
161	0.539†
162	0.603
163	0.528
164	0.555
165	0.558†
166	0.618†
167	0.467†
168	1.39†
169	1.21†
170	1.31†
171	0.598†
172	0.479†
173	0.908†
174	0.484†
175	0.381†
176	0.547†
177	0.67†
178	0.55†
179	0.655†
180	0.756
181	0.656
182	0.574†
183	1.52†
184	1.28
185	0.993
186	0.524†
187	1.22†
188	0.513†
189	0.349†
190	n/a
191	1.17
192	0.291†
193	1.27
194	0.600†
195	0.604
196	0.696
197	0.889
198	0.631
199	1.13
200	1.2

Cmpd No.	APOL1 G2 FLIPR AC_{50} (μM)
201	0.909†
202	1.72†
203	1.19
204	0.869†
205	1.22†
206	n/a
207	n/a
208	1.55
209	1.24†
210	1.54
211	1.29
212	1.36
213	1.12†
214	0.355
215	1.13
216	3.14†
217	0.866†
218	0.69†
219	0.835
220	0.679†
221	0.598
222	0.783
223	0.311†
224	0.83
225	0.847
226	1.08†
227	1.11†
228	1.20†
229	0.792†
230	0.891†
231	1.02†
232	1.01
233	1.16
234	0.786†
235	1.00†
236	0.634
237	3.31
238	0.285†
239	1.54
240	n/a

Cmpd No.	APOL1 G2 FLIPR AC_{50} (μM)
241	n/a
242	n/a
243	n/a
244	1.06
245	0.718
246	1.34
247	0.806†
248	0.82
249	0.433†
250	0.559
251	0.546†
252	1.35†
253	1.22†
254	0.898†
255	2.64†
256	0.261†
257	0.974†
258	1.05†
259	0.651
260	1.38
261	1.46
262	2.39†
263	2.54
264	1.95†
265	0.697
266	0.862
272	0.921
273	2.10
274	0.722
275	0.640
276	1.75
277	n/a
278	0.769
279	n/a
280	n/a
281	1.31
282	n/a
283	2.00
284	0.756
285	0.714

Cmpd No.	APOL1 G2 FLIPR AC_{50} (μM)
286	0.917
287	0.303
288	0.369
289	0.552
290	0.253
291	1.19
292	1.30
293	n/a
294	n/a
295	n/a
296	n/a
297	0.937
298	n/a
299	n/a
300	0.674
301	0.586
302	1.03
303	0.822
304	1.01
305	0.649
306	1.40
307	0.320
308	n/a
309	n/a
310	n/a
311	n/a
312	n/a
313	n/a
314	0.968
315	0.330
316	1.15
317	0.792
318	n/a
319	0.378
320	0.787
321	0.621
322	0.588
323	0.400
324	0.942
325	0.791

Cmpd No.	APOL1 G2 FLIPR AC_{50} (μM)
326	0.680
327	0.452
328	0.748
329	n/a
330	n/a
331	n/a
332	n/a
333	0.486
334	2.00
335	n/a
336	n/a
338	n/a
339	n/a
340	n/a
341	1.06
342	0.780
343	0.437
344	n/a
345	0.469
346	0.557
347	n/a
348	n/a
349	0.199
350	0.113
351	n/a
352	0.597
353	n/a
354	n/a
355	n/a
356	2.49
357	0.412
358	n/a
359	n/a
360	n/a
361	n/a
362	n/a
363	n/a
364	n/a
365	n/a
366	n/a

Cmpd No.	APOL1 G2 FLIPR AC_{50} (μM)
367	n/a
368	n/a
369	n/a
370	n/a
371	0.504
372	n/a
373	n/a
374	n/a
375	n/a
376	n/a
377	n/a
378	n/a
379	n/a
380	n/a
381	n/a
382	n/a
383	n/a
384	n/a
385	n/a
386	n/a
387	n/a
388	n/a
389	n/a
390	n/a
391	n/a
392	n/a
393	1.06
394	0.250
395	n/a
396	0.531
397	0.416
398	n/a
399	n/a
400	n/a
401	0.603†
402	n/a
403	n/a
404	n/a
405	n/a
406	n/a

Cmpd No.	APOL1 G2 FLIPR AC_{50} (μM)
407	n/a
408	0.283†
409	n/a
410	0.623†
411	0.436†
412	2.9†
413	0.251†
414	0.347†
415	0.319†
416	0.449†
417	0.343†
418	0.309†
419	0.383†
420	0.892†
421	0.564†
422	n/a
423	0.284†
424	0.895†
425	1.1†
426	0.597
427	0.708†
428	1.2†

Cmpd No.	APOL1 G2 FLIPR AC_{50} (μM)
429	0.435†
430	0.518†
431	4.87†
432	2.56†
433	1.3†
434	1.27†
435	1.17
436	n/a
437	0.612†
438	n/a
439	0.603
440	0.552
441	n/a
442	2.14†
443	2.67†
444	n/a
445	1.11
446	1.18†
447	1.13
448	1.14†
449	0.609†
450	2.27†

Cmpd No.	APOL1 G2 FLIPR AC_{50} (μM)
451	0.459†
452	n/a
453	0.935†
454	0.473†
455	1.25†
456	1.01†
457	n/a
458	0.528†
459	0.37†
460	0.317†
461	0.676†
462	0.943†
463	2.84†
464	1.19†
465	0.748†
466	n/a
467	n/a
468	0.867
469	n/a
470	1.11†
471	n/a
472	n/a

Example B2

[1425] This example shows that the compounds of the present disclosure are able to reduce cell death caused by overexpression of APOL1.

[1426] A HEK293 clonal cell line overexpressing APOL1 G2 (HEK293/T-REx APOL1 G2/clone #2) was maintained in 1x DMEM-GlutaMax (Gibco, 10569-010) media with 10% tetracycline-free FBS (Takara Bio USA, 631101), 5 μg/mL Blasticidin (Gibco, A1113903), and 100 μg/mL Zeocin (Invitrogen, R25001) in T75 flasks. In preparation for the assay, this media was aspirated and 2 mL of prewarmed TrypLE Express (Gibco, 12605-010) was added to a flask to detach cells. The flask was then incubated (humidified, 37˚C with 5% CO_2) for 3-5 minutes. Afterwards, 8 mL of prewarmed cell assay media (1x DMEM-GlutaMax media with 10% tetracycline-free FBS) was added to the trypsinized cells. The suspension was gently mixed, and

cells were counted using a Countess Cell Counting Chamber (Invitrogen). The suspension was diluted using cell assay media to generate a working stock solution (166,667 cells/mL). Using a MultiDrop Combi (Thermo Electron Corp), 30 µL (final cell density = 5,000 cells/well) of the working stock solution was dispensed into each well of white 384-well assay ready plates (Nunc™, 164610) containing 6 ng/mL doxycycline, to induce APOL1 expression, and compound. All compounds were plated in a duplicate 8-point dilution series that consisted of 3-fold stepwise dilutions (0.5% DMSO final). Assay plates were incubated (humidified, 37°C with 5% CO_2) for 17 hours. After the incubation, the plates were equilibrated at room temperature for 1 hour. Next, 15 µl of CellTiter-Glo® reagent (Promega, G7570) was added to each well using a MultiDrop Combi. Plates were placed on an orbital shaker (500 rpm) for 5 minutes to induce cell lysis and then incubated at room temperature for 10 minutes. Luminescence was measured on an Envision plate reader. Collaborative Drug Discovery software was utilized for graphing data. Plots were generated using a four parameter logistic curve fit.

[1427] Table 40 below provides the results from this experiment. Unless otherwise specified, EC_{50} values are reported as the geometric mean of at least 2 assay runs on separate days. Each run represents the average of a technical replicate, where each compound was assayed twice in the same plate. A superscript † symbol indicates a value from the average of a technical replicate from a single assay run, where each compound was assayed twice in the same plate. Compounds in Table 40 are referred to by the corresponding Compound Number in Table 1, which is also referred to in the synthetic examples. When one or more of the numbered compounds are identified by stereochemistry (for example, (*R*)- or (*S*)-), the specific stereoisomer for which data is provided in Table 40 may be identified by the elution order of such compound as described in the synthetic examples. Absolute stereochemistry of such compounds may be identified by methods known in the art. For Table 40 below, n/a represents "not available".

[1428] Rescue EC_{50} values reported in Table 40 below represent the half-maximal effective concentration for reversal of cell death caused by overexpression of APOL1. This example demonstrates that compounds of the present disclosure are able to reduce cell death caused by overexpression of APOL1 at sub micromolar concentration.

Table 40.

Cmpd No.	APOL1 G2 HEK293 Rescue EC_{50} (μM)
1	0.120†
2	0.134†
3	0.142†
4	0.0719
5	0.213
6	0.121
7	0.279
8	0.598
9	1.76
10	0.0903
11	1.70
12	0.307
13	3.01
14	0.13
15	0.124
16	0.112
17	0.060
18	0.225
19	0.794
20	0.294
21	1.27
22	0.232
23	0.135
24	0.24
25	1.31
26	1.76
27	0.062
28	0.799
29	1.42
30	1.48
31	0.81
32	0.785
33	1.07
34	1.33
35	0.574
36	0.919
37	1.28
38	0.059
39	0.0567

Cmpd No.	APOL1 G2 HEK293 Rescue EC_{50} (μM)
40	0.072
41	0.097
42	0.343
43	0.0331
44	0.116
45	0.122
46	0.0728
47	0.148
48	0.199
49	0.0664
50	0.0249
51	0.214
52	0.214
53	0.0529
54	0.0903
55	0.983
56	0.105
57	0.19
58	1.31
59	0.213
60	0.0627
61	0.267
62	0.165
63	0.0511
64	0.163
65	0.0875
66	0.108
67	0.802
68	0.148
69	0.0826
70	1.05
71	0.345
72	0.0359†
73	0.527
74	0.167
75	0.114
76	0.0477
77	2.25
78	0.041

Cmpd No.	APOL1 G2 HEK293 Rescue EC_{50} (μM)
79	0.207
80	0.0657
81	0.28
82	0.0722
83	0.247
84	0.0649
85	0.0703
86	0.0465
87	0.103
88	0.121
89	0.0557
90	0.151
91	0.0245
92	0.0515
93	0.0909
94	0.14
95	0.246
96	0.0505
97	0.0446
98	0.0544†
99	0.0865
100	0.0465
101	0.0496
102	0.0314
103	0.0494
104	0.139
105	0.0407
106	0.0335
107	0.0308
108	0.0169
109	0.0969
110	0.0413
111	0.142
112	0.0472
113	0.0836
114	0.0465
115	0.0949
116	0.0818
117	0.0815

Cmpd No.	APOL1 G2 HEK293 Rescue EC_{50} (μM)
118	0.431
119	0.435
120	0.324
121	0.0812
122	0.0875
123	0.0795
124	0.297
125	0.355
126	0.273
127	0.0208
128	0.0427
129	0.0246
130	0.0923
131	0.068
132	0.153
133	0.203
134	0.199
135	0.211
136	0.0224
137	0.114
138	0.0782
139	0.133
140	0.172
141	0.048
142	0.0483
143	0.0369
144	0.081
145	0.0504
146	0.121
147	0.0631
148	0.107
149	0.101
150	0.228
151	0.397
152	0.405
153	0.0221
154	0.0671
155	0.0262
156	0.0559

Cmpd No.	APOL1 G2 HEK293 Rescue EC_{50} (μM)
157	0.0504
158	0.0657
159	0.168
160	0.0754
161	0.0464
162	0.0571
163	0.0246
164	0.103
165	0.0212†
166	0.0561†
167	0.0427†
168	0.343†
169	0.247
170	0.803†
171	0.100†
172	0.0991†
173	0.289†
174	0.104†
175	0.0631†
176	0.0469†
177	0.0782†
178	0.256†
179	0.164†
180	0.0221
181	0.0445
182	0.0996†
183	0.702†
184	0.498
185	0.113
186	0.0359†
187	0.268†
188	0.0392†
189	0.0591†
190	0.0547
191	0.13
192	0.0411
193	0.155
194	0.246
195	0.0394

Cmpd No.	APOL1 G2 HEK293 Rescue EC_{50} (μM)
196	0.0919
197	0.0323
198	0.0631
199	0.148
200	0.0872
201	0.609
202	0.315
203	0.187
204	1.55
205	0.472
206	> 9.54
207	> 10.0
208	0.238
209	3.07
210	0.0633
211	0.138
212	0.0814
213	0.189
214	0.079
215	0.0798
216	0.281
217	0.0326
218	0.0256
219	0.0263
220	0.053
221	0.0474
222	0.141
223	0.0978
224	0.0386
225	0.0326
226	0.043
227	0.047
228	0.101
229	0.128
230	0.0987
231	0.042
232	0.0392
233	0.0577
234	0.0803

Cmpd No.	APOL1 G2 HEK293 Rescue EC_{50} (μM)
235	0.0598
236	0.045
237	0.238
238	0.0852
239	0.0779
240	0.0526
241	0.0721
242	0.074
243	0.046
244	0.0704
245	0.139
246	0.562
247	0.092
248	0.0584
249	0.0268†
250	0.0492†
251	0.125†
252	0.471†
253	0.608†
254	0.175†
255	0.353†
256	0.0446†
257	0.256†
258	0.444†
259	0.0375
260	0.119
261	0.089
262	0.299
263	0.198
264	2.25
265	0.030
266	0.104
267	0.0378
268	0.0534
269	0.102
270	0.0256
271	0.152
272	0.0934
273	0.0885

Cmpd No.	APOL1 G2 HEK293 Rescue EC_{50} (μM)
274	0.034
275	0.027
276	0.101
277	0.034
278	0.023
279	0.060
280	0.080
281	0.056
282	0.130
283	0.099
284	0.199
285	0.200
286	0.181
287	0.0335
288	0.0341
289	0.0167
290	0.0182
291	0.0264
292	0.0232
293	0.294
294	0.0233
295	0.0436
296	0.0773
297	0.0318
298	0.0818
299	0.0213
300	0.10
301	0.086
302	0.0981
303	0.156
304	0.134
305	0.0854
306	0.110
307	0.0204
308	0.112
309	0.0559
310	0.103
311	0.0383
312	0.0243

Cmpd No.	APOL1 G2 HEK293 Rescue EC_{50} (μM)
313	0.0633
314	0.0243
315	0.0257
316	0.0327
317	0.0239
318	0.0232
319	0.0419
320	0.0221
321	0.0241
322	0.0185
323	0.0173
324	0.0256
325	0.0864
326	0.0312
327	0.0289
328	0.0341
329	0.0569
330	0.668
331	0.166
332	n/a
333	0.043
334	0.110
335	n/a
336	n/a
338	0.0994
339	0.0366
340	0.0302
341	0.0415
342	0.0902
343	0.162
344	0.194
345	0.0364
346	0.0343
347	n/a
348	n/a
349	0.0254
350	0.0188
351	0.166
352	0.0086

Cmpd No.	APOL1 G2 HEK293 Rescue EC_{50} (μM)
353	0.0123
354	0.0146
355	n/a
356	0.0506
357	0.0223
358	0.065
359	n/a
360	n/a
361	n/a
362	n/a
363	n/a
364	0.112
365	n/a
366	0.080
367	0.0877
368	n/a
369	n/a
370	n/a
371	0.0172
372	n/a
373	0.0534
374	0.101
375	n/a
376	0.0469
377	0.0859
378	0.388
379	0.842
380	n/a
381	n/a
382	n/a
383	n/a
384	n/a
385	n/a
386	n/a
387	n/a
388	n/a
389	n/a
390	n/a
391	n/a

Cmpd No.	APOL1 G2 HEK293 Rescue EC_{50} (μM)
392	0.0271
393	0.0805
394	0.024
395	0.0868
396	0.0405
397	0.0459
398	0.0201
399	0.0498
400	0.224
401	0.0367
402	0.0238
403	0.0957
404	0.129
405	0.00959
406	0.0583
407	0.0241
408	0.0231
409	0.0702
410	0.0641
411	0.0226
412	0.0453
413	0.0603
414	0.0367
415	0.0203
416	0.169
417	0.0492
418	0.0785
419	0.0309
420	0.0647
421	0.0345
422	0.0635
423	0.0593
424	0.0502
425	0.0906
426	0.0378
427	0.0185
428	0.0543
429	0.13
430	0.0729

Cmpd No.	APOL1 G2 HEK293 Rescue EC_{50} (μM)
431	0.0187
432	0.161
433	0.0148
434	0.0112
435	0.0129
436	0.0801
437	0.112
438	0.204
439	0.0149
440	0.0544
441	0.0574
442	< 3.08E-03
443	0.0102
444	0.0224
445	0.00815
446	0.0332
447	0.0341†
448	0.112†
449	0.102
450	0.0055
451	0.0321
452	0.0282
453	0.0191
454	0.0241
455	0.0753
456	0.0282
457	0.278
458	0.0165
459	0.029
460	0.0541
461	0.0281
462	0.0178
463	0.00584
464	0.00502
465	0.00886
466	0.00426
467	0.00474
468	0.00645
469	0.0199

Cmpd No.	APOL1 G2 HEK293 Rescue EC_{50} (μM)
470	0.179

Cmpd No.	APOL1 G2 HEK293 Rescue EC_{50} (μM)
471	> 3.30

Cmpd No.	APOL1 G2 HEK293 Rescue EC_{50} (μM)
472	n/a

Example B3

[1429] This example shows that the compounds of the present disclosure are able to reduce cell death caused by overexpression of APOL1.

[1430] Compounds were also assayed in a HEK293 clonal cell line overexpressing APOL1 G1 by a method similar to that shown in Example B2 above.

[1431] Table 41 below provides the results from this experiment. Unless otherwise specified, EC_{50} values are reported as the geometric mean of at least 2 assay runs on separate days. Each run represents the average of a technical replicate, where each compound was assayed twice in the same plate. A superscript † symbol indicates a value from the average of a technical replicate from a single assay run, where each compound was assayed twice in the same plate. A ¥ symbol represents compound concentration at 50% rescue estimated due to lack of sigmoidal curve preventing curve fitting. Compounds in Table 41 are referred to by the corresponding Compound Number in Table 1, which is also referred to in the synthetic examples. When one or more of the numbered compounds are identified by stereochemistry (for example, (*R*)- or (*S*)-), the specific stereoisomer for which data is provided in Table 41 may be identified by the elution order of such compound as described in the synthetic examples. Absolute stereochemistry of such compounds may be identified by methods known in the art. For Table 41 below, n/a represents “not available”.

[1432] Rescue EC_{50} values reported in Table 41 below represent the half-maximal effective concentration for reversal of cell death caused by overexpression of APOL1. This example demonstrates that compounds of the present disclosure are able to reduce cell death caused by overexpression of APOL1 at sub micromolar concentration.

Table 41.

Cmpd No.	APOL1 G1 HEK293 Rescue EC_{50} (μM)
1	0.302
2	0.346
3	0.257
4	0.177
5	0.295
6	0.252
7	0.764
8	1.44
9	11.5¥
10	0.444
11	2.3
12	1.14
13	> 30.0
14	0.476
15	0.279
16	0.295
17	0.16
18	0.663
19	4.81
20	0.815
21	> 14.4
22	0.58
23	0.449
24	0.609
25	8.3¥
26	10.9¥
27	0.186
28	0.655
29	5.56
30	> 22.5
31	1.57
32	1.86
33	> 3.47

Cmpd No.	APOL1 G1 HEK293 Rescue EC_{50} (μM)
34	> 1.96
35	0.488
36	> 2.15
37	0.692
38	0.222
39	> 0.247
40	0.294
41	0.307
42	1.08
43	0.131
44	0.478
45	0.387
46	0.253
47	0.399
48	0.445
49	0.26
50	0.0911
51	1.25
52	1.06
53	0.219
54	0.386
55	1.21
56	0.33
57	0.39
58	2.12
59	0.422
60	0.183
61	0.632
62	0.433
63	0.16
64	0.516
65	0.351
66	0.323

Cmpd No.	APOL1 G1 HEK293 Rescue EC_{50} (μM)
67	2.86
68	0.368
69	0.311
70	> 2.53
71	1.34
72	0.161
73	3.52
74	0.471
75	0.406
76	0.19
77	> 4.76
78	0.128
79	0.533
80	0.178
81	0.948
82	0.252
83	0.788
84	0.233
85	0.157
86	0.126
87	0.281
88	0.438
89	0.138
90	0.594
91	0.099
92	0.101
93	0.23
94	0.21
95	0.457
96	0.148
97	0.143
98	0.183
99	0.205

Cmpd No.	APOL1 G1 HEK293 Rescue EC_{50} (μM)
100	0.134
101	0.248
102	0.111
103	0.124
104	0.356
105	0.175
106	0.122
107	0.12
108	0.0497
109	0.321
110	0.1
111	0.246
112	0.0775
113	0.176
114	0.128
115	0.199
116	0.234
117	0.174
118	2.1¥
119	3.4¥
120	> 5.23
121	0.249
122	0.188
123	0.232
124	0.92
125	> 4.86
126	1.01
127	0.061
128	0.158
129	0.0728
130	0.253
131	0.186
132	0.685

Cmpd No.	APOL1 G1 HEK293 Rescue EC_{50} (μM)
133	0.885
134	0.991
135	1.14
136	0.0494
137	0.249
138	0.253
139	0.383
140	0.6
141	0.204
142	0.192
143	0.125
144	0.246
145	0.0985
146	0.221
147	0.183
148	0.282
149	0.246
150	1.54
151	2.5¥
152	> 4.17
153	0.0962
154	0.252
155	0.067
156	0.153
157	0.152
158	0.252
159	0.588
160	0.244
161	0.135
162	0.174
163	0.113
164	0.316
165	0.059

Cmpd No.	APOL1 G1 HEK293 Rescue EC_{50} (μM)
166	0.163
167	0.138
168	> 7.84
169	1.03
170	2.3¥
171	0.228
172	0.188
173	1.16†
174	0.253
175	0.153
176	0.157
177	0.132
178	1.19†
179	0.484
180	0.0749
181	0.194
182	0.225
183	5.8¥
184	2.5¥
185	0.231
186	0.0988
187	1.26
188	0.122
189	0.148
190	0.105
191	0.283
192	0.126
193	0.377
194	0.414
195	0.072
196	0.207
197	0.0695
198	0.203

Cmpd No.	APOL1 G1 HEK293 Rescue EC_{50} (μM)
199	0.312
200	0.203
201	4.92
202	2.55
203	0.457
204	1.27
205	1.76
206	4.31
207	> 10.0
208	0.554
209	> 2.84
210	0.153
211	0.38
212	0.192
213	0.497
214	0.169
215	0.122
216	1¥
217	0.108
218	0.125
219	0.116
220	0.301
221	0.217
222	0.605
223	0.326
224	0.155
225	0.0517
226	0.138
227	0.21
228	0.426
229	0.396
230	0.325
231	0.169

Cmpd No.	APOL1 G1 HEK293 Rescue EC_{50} (μM)
232	0.137
233	0.244
234	0.233
235	0.268
236	0.134
237	>3.25
238	0.244
239	0.191
240	0.282
241	0.217
242	0.316
243	0.208
244	0.189
245	0.301
246	4.86
247	0.27
248	0.219
249	0.0706
250	0.192
251	0.323†
252	1.8¥
253	4.4¥
254	2.04
255	2.9¥
256	0.116
257	1¥
258	1.3¥
259	0.0925
260	0.248
261	0.167
262	1.78
263	0.462
264	10¥

Cmpd No.	APOL1 G1 HEK293 Rescue EC_{50} (μM)
265	0.132
266	0.353
267	0.137
268	0.211
269	0.325
270	0.0607
271	0.34
272	0.148
273	0.206
274	0.0999
275	0.0627
276	0.228
277	0.117
278	0.0926
279	0.234
280	0.235
281	0.164
282	0.383
283	0.211
284	0.775
285	0.292
286	0.272
287	0.0858
288	0.0621
289	0.0506
290	0.0639
291	0.104
292	0.0515
293	0.193†
294	0.0656
295	0.112
296	0.159
297	0.119

Cmpd No.	APOL1 G1 HEK293 Rescue EC_{50} (μM)
298	0.218
299	0.0636
300	0.183
301	0.19
302	0.236
303	0.351
304	0.286
305	0.172
306	0.245
307	0.07
308	0.196
309	0.134
310	0.267
311	0.1
312	0.0665
313	0.135
314	0.0532
315	0.086
316	0.0994
317	0.0456
318	0.0659
319	0.118
320	0.0539
321	0.0477
322	0.0386
323	0.0364
324	0.0408
325	0.197
326	0.104
327	0.0844
328	0.0982
329	0.0961
330	1.5[¥]

Cmpd No.	APOL1 G1 HEK293 Rescue EC_{50} (μM)
331	0.44
332	10[¥]
333	0.0986
334	0.269
335	n/a
336	n/a
338	0.213
339	n/a
340	n/a
341	n/a
342	n/a
343	0.431
344	0.254
345	0.079
346	0.0837
347	n/a
348	n/a
349	0.0735
350	0.0439
351	0.299
352	0.00995
353	0.0345
354	0.0401
355	n/a
356	0.162[†]
357	0.0353
358	0.111
359	n/a
360	n/a
361	n/a
362	n/a
363	n/a
364	0.239

Cmpd No.	APOL1 G1 HEK293 Rescue EC_{50} (μM)
365	n/a
366	0.136
367	0.145
368	n/a
369	n/a
370	n/a
371	0.0288
372	n/a
373	0.133
374	0.216
375	n/a
376	0.129
377	0.172
378	1[¥]
379	>10
380	n/a
381	n/a
382	n/a
383	n/a
384	n/a
385	n/a
386	n/a
387	n/a
388	n/a
389	n/a
390	n/a
391	n/a
392	0.0899
393	0.159
394	0.0777
395	0.157
396	0.085
397	0.105

Cmpd No.	APOL1 G1 HEK293 Rescue EC_{50} (μM)
398	0.374
399	0.117
400	0.678
401	0.0682
402	0.0357
403	0.144
404	0.247
405	0.0192
406	0.109
407	0.0463
408	0.056
409	0.136
410	0.0933
411	0.0556
412	0.0707
413	0.208
414	0.11
415	0.0692
416	0.382
417	0.104
418	0.215
419	0.108
420	0.144
421	0.0833
422	0.165

Cmpd No.	APOL1 G1 HEK293 Rescue EC_{50} (μM)
423	0.116
424	0.112
425	0.271
426	0.0803
427	0.0358
428	0.0896
429	0.2
430	0.123
431	0.037
432	0.288
433	0.0296
434	0.0148
435	0.0384
436	0.114
437	0.186
438	0.242
439	0.0455
440	0.139
441	0.0961
442	0.0156
443	0.0308
444	0.0723
445	0.0294
446	0.0825
447	0.0643

Cmpd No.	APOL1 G1 HEK293 Rescue EC_{50} (μM)
448	0.687
449	0.247
450	0.0149
451	0.115
452	0.0844
453	n/a
454	n/a
455	n/a
456	0.0982
457	> 3.30
458	0.0757
459	0.0955
460	0.0977
461	0.0809
462	0.0534
463	0.0132
464	n/a
465	n/a
466	0.00871
467	0.0143
468	0.0145
469	0.0487
470	0.0476
471	> 3.30
472	n/a

Example B4

[1433] APOL1 G2 human immortalized podocyte viability assay for measurement of cytotoxicity reversal by compound (APOL1 G2 podocyte cell rescue assay). This example shows that the compounds of the present disclosure are able to reverse cytotoxicity in human immortalized podocytes.

[1434] Cell Handling. The hTERT-immortalized kidney podocyte cell line was procured from the laboratory of Dr. Moin Saleem at the University of Bristol, UK (Nephrology 17 (2012) 525–531; doi:10.1111/j.1440-1797.2012.01619.x; herein incorporated by reference in its entirety). Parental and engineered cell lines were cultured in RPMI 1640 media (Gibco, 11875093) with 10% Tet System Approved FBS (Takara, 631101). The engineered cell line was maintained under selection (2.5 μg/mL puromycin). Cell lines were maintained and engineered at 33°C. Cell cultures were transferred to 37°C for 10 to 14 days to initiate differentiation (Nephrology 17 (2012) 525–531; doi:10.1111/j.1440-1797.2012.01619.x; herein incorporated by reference in its entirety). During this time, media was refreshed every 3 days. After differentiation, cells engineered to inducibly express APOL1 G2 were used in the podocyte cell rescue assay.

[1435] Cell Line Engineering. The APOL1 G2 coding sequence was cloned into the pLVX-TetOne-Puro vector and verified by sequencing (Genscript Biotech). This construct was designed to have a C-terminal HiBiT tag. Lentiviral packaging of the vector was conducted using the Lenti-X Packaging Single Shots (VSVG) system according to manufacturer instructions (Takara Bio, 631275). A stable cell line was generated by transfecting the parental podocyte cell line with the concentrated virus in media with 5 μg/mL polybrene (Sigma, TR-1003-G). Media was changed the following day. 72 hours post transfection, 2.5 μg/mL puromycin (Gibco, A1113803) was added to the cells and cells were maintained in selection media thereafter. This APOL1 G2 stable cellular pool was subjected to a stringent limiting dilution to generate a pure stable clone (Podocyte/pLVX-TetOne APOL1 G2/clone D10) capable of inducible expression of APOL1 G2.

[1436] Assay Setup. T175 flasks containing differentiated podocytes engineered to inducibly express APOL1 G2 (Podocyte/ pLVX-TetOne APOL1 G2/clone D10) were washed once with 15 mL of DPBS (Thermo Fisher, 14190-144). These flasks were each trypsinized with 3 mL of prewarmed TrypLE Express (Gibco, 12605-010) and incubated at 37°C with 5% CO_2 until cells detached and neutralized with 7 mL of prewarmed assay media (RPMI 1640 media with 10% Tet System Approved FBS, no selection agent). Cells were pooled and the resulting suspension was gently mixed. The cell suspension was counted using a Countess Cell Counting Chamber (Invitrogen) and the cell concentration was adjusted to 240,000 cells/mL using assay media. Next, 25μL of a 480 ng/mL working stock of doxycycline diluted in assay media was added to an assay ready plate. All experiments were performed in 384-well, white, solid bottom, tissue culture treated

plates (Greiner, 781080). The assay ready compound plates were generated with duplicate 8-point compound dilution series that consisted of 3-fold stepwise dilutions (0.4% DMSO final). The plates were centrifuged at 1000 rpm for 1 minute. 25μL of diluted cell suspension (final cell density = 6,000 cells/well) was added to each well. The plates were centrifuged again at 1000rpm for 1 minute and then incubated in a humidified incubator (37°C with 5% CO_2). After 95 hours, the assay plates were removed from the incubator and allowed to equilibrate to room temperature for 1 hour. CellTiter-Glo® reagent (Promega, G7570) was prepared according to the manufacturer's instructions. 25 μL of CellTiter-Glo® reagent was added to each well. Assay plates were sealed with foil and mixed for 5 minutes on an orbital shaker (500 rpm) to induce cell lysis. Plates were centrifuged at 1000 rpm for 1 minute. 10 minutes after CellTiter-Glo® reagent addition, an Envision plate reader (Perkin Elmer) was used to measure the luminescent signal of each assay plate. Collaborative Drug Discovery software was utilized for graphing data.

[1437] Table 42 below provides the results from this experiment. Unless otherwise specified, EC_{50} values are reported as the geometric mean of at least 2 assay runs on separate days. Each run represents the average of a technical replicate, where each compound was assayed twice in the same plate. A superscript † symbol indicates a value from the average of a technical replicate from a single assay run, where each compound was assayed twice in the same plate. Compounds in Table 42 are referred to by the corresponding Compound Number in Table 1, which is also referred to in the synthetic examples. When one or more of the numbered compounds are identified by stereochemistry (for example, (*R*)- or (*S*)-), the specific stereoisomer for which data is provided in Table 42 may be identified by the elution order of such compound as described in the synthetic examples. Absolute stereochemistry of such compounds may be identified by methods known in the art. For Table 42 below, n/a represents "not available".

[1438] Rescue EC_{50} values reported in Table 42 below represent the half-maximal effective concentration for reversal of cell death caused by overexpression of APOL1. This example demonstrates that compounds of the present disclosure are able to reduce cell death caused by overexpression of APOL1 at sub micromolar concentration.

Table 42.

Cmpd No.	APOL1 G2 Podocyte Rescue EC_{50} (μM)
1	0.0188
2	0.0107
3	0.0235
4	0.00916
5	>0.330
6	0.0477
7	n/a
8	n/a
9	n/a
10	n/a
11	n/a
12	n/a
13	n/a
14	n/a
15	n/a
16	n/a
17	n/a
18	n/a
19	n/a
20	n/a
21	n/a
22	n/a
23	n/a
24	0.0374
25	n/a
26	n/a
27	n/a
28	n/a
29	n/a
30	n/a
31	n/a
32	n/a
33	n/a
34	n/a
35	n/a
36	n/a
37	n/a
38	n/a
39	n/a

Cmpd No.	APOL1 G2 Podocyte Rescue EC_{50} (μM)
40	n/a
41	n/a
42	n/a
43	n/a
44	n/a
45	n/a
46	n/a
47	n/a
48	n/a
49	n/a
50	n/a
51	n/a
52	n/a
53	n/a
54	n/a
55	n/a
56	n/a
57	n/a
58	n/a
59	n/a
60	n/a
61	n/a
62	n/a
63	n/a
64	n/a
65	n/a
66	n/a
67	n/a
68	n/a
69	n/a
70	n/a
71	n/a
72	n/a
73	n/a
74	n/a
75	n/a
76	n/a
77	n/a
78	n/a

Cmpd No.	APOL1 G2 Podocyte Rescue EC_{50} (μM)
79	n/a
80	n/a
81	n/a
82	n/a
83	n/a
84	n/a
85	n/a
86	n/a
87	n/a
88	n/a
89	n/a
90	n/a
91	n/a
92	n/a
93	n/a
94	n/a
95	n/a
96	n/a
97	n/a
98	n/a
99	n/a
100	n/a
101	n/a
102	n/a
103	n/a
104	n/a
105	n/a
106	n/a
107	n/a
108	n/a
109	n/a
110	n/a
111	n/a
112	n/a
113	n/a
114	n/a
115	n/a
116	n/a
117	n/a

Cmpd No.	APOL1 G2 Podocyte Rescue EC_{50} (μM)
118	n/a
119	n/a
120	n/a
121	n/a
122	n/a
123	n/a
124	n/a
125	n/a
126	n/a
127	0.00539
128	n/a
129	n/a
130	n/a
131	n/a
132	n/a
133	n/a
134	n/a
135	n/a
136	n/a
137	n/a
138	n/a
139	n/a
140	n/a
141	n/a
142	n/a
143	n/a
144	n/a
145	n/a
146	n/a
147	n/a
148	n/a
149	n/a
150	n/a
151	n/a
152	n/a
153	n/a
154	n/a
155	n/a
156	n/a

Cmpd No.	APOL1 G2 Podocyte Rescue EC_{50} (μM)
157	n/a
158	n/a
159	n/a
160	n/a
161	n/a
162	n/a
163	n/a
164	n/a
165	n/a
166	n/a
167	n/a
168	n/a
169	n/a
170	n/a
171	n/a
172	n/a
173	n/a
174	n/a
175	n/a
176	n/a
177	n/a
178	n/a
179	n/a
180	n/a
181	n/a
182	n/a
183	n/a
184	n/a
185	n/a
186	n/a
187	n/a
188	n/a
189	n/a
190	n/a
191	n/a
192	n/a
193	n/a
194	n/a
195	n/a

Cmpd No.	APOL1 G2 Podocyte Rescue EC_{50} (μM)
196	n/a
197	n/a
198	n/a
199	n/a
200	n/a
201	n/a
202	n/a
203	n/a
204	n/a
205	n/a
206	n/a
207	n/a
208	n/a
209	n/a
210	n/a
211	n/a
212	n/a
213	n/a
214	n/a
215	n/a
216	n/a
217	n/a
218	n/a
219	n/a
220	n/a
221	n/a
222	n/a
223	n/a
224	n/a
225	n/a
226	n/a
227	n/a
228	n/a
229	n/a
230	n/a
231	n/a
232	0.00217
233	0.00425
234	n/a

Cmpd No.	APOL1 G2 Podocyte Rescue EC_{50} (μM)
235	n/a
236	n/a
237	n/a
238	n/a
239	0.0021
240	0.0139
241	n/a
242	0.0197
243	0.00411
244	n/a
245	n/a
246	n/a
247	n/a
248	n/a
249	n/a
250	n/a
251	n/a
252	n/a
253	n/a
254	n/a
255	n/a
256	n/a
257	n/a
258	n/a
259	0.00121
260	0.0103
261	0.00229†
262	n/a
263	n/a
264	n/a
265	n/a
266	n/a
267	0.00663
268	n/a
269	0.0304
270	0.00292
271	n/a
272	0.001†
273	0.0052

Cmpd No.	APOL1 G2 Podocyte Rescue EC_{50} (μM)
274	0.0188
275	0.00389
276	0.0104
277	n/a
278	n/a
279	n/a
280	n/a
281	n/a
282	n/a
283	0.00508
284	0.105
285	n/a
286	n/a
287	0.0177
288	0.0195†
289	0.00222
290	0.00276†
291	n/a
292	n/a
293	n/a
294	n/a
295	n/a
296	n/a
297	n/a
298	n/a
299	n/a
300	0.0333
301	0.0669
302	n/a
303	n/a
304	n/a
305	0.015
306	0.00194
307	0.00261†
308	n/a
309	n/a
310	n/a
311	n/a
312	n/a

Cmpd No.	APOL1 G2 Podocyte Rescue EC_{50} (μM)
313	n/a
314	0.00457†
315	n/a
316	n/a
317	0.00292
318	n/a
319	n/a
320	n/a
321	0.00765
322	n/a
323	0.00202
324	n/a
325	n/a
326	n/a
327	n/a
328	n/a
329	n/a
330	n/a
331	0.0857†
332	n/a
333	n/a
334	0.00958†
335	n/a
336	n/a
338	n/a
339	n/a
340	n/a
341	n/a
342	n/a
343	n/a
344	n/a
345	0.0158
346	0.0388
347	n/a
348	n/a
349	0.00681
350	0.0103
351	n/a
352	0.00112

Cmpd No.	APOL1 G2 Podocyte Rescue EC_{50} (μM)
353	n/a
354	n/a
355	n/a
356	0.0215
357	0.00404
358	0.024
359	n/a
360	n/a
361	n/a
362	n/a
363	n/a
364	n/a
365	n/a
366	n/a
367	n/a
368	n/a
369	n/a
370	n/a
371	0.0011
372	n/a
373	n/a
374	n/a
375	n/a
376	0.00621
377	0.0244
378	n/a
379	n/a
380	n/a
381	n/a
382	n/a
383	n/a
384	n/a
385	n/a
386	n/a
387	n/a
388	n/a
389	n/a
390	n/a
391	n/a

Cmpd No.	APOL1 G2 Podocyte Rescue EC_{50} (μM)
392	n/a
393	0.023
394	0.0169
395	0.137
396	0.0186
397	0.0143
398	n/a
399	n/a
400	n/a
401	0.00462
402	n/a
403	n/a
404	n/a
405	n/a
406	n/a
407	n/a
408	0.00705
409	n/a
410	n/a
411	0.00145
412	n/a
413	n/a
414	n/a
415	n/a
416	n/a
417	n/a
418	n/a
419	n/a
420	n/a
421	n/a
422	n/a
423	n/a
424	n/a
425	n/a
426	0.0041
427	0.00195
428	0.0122
429	n/a
430	n/a

Cmpd No.	APOL1 G2 Podocyte Rescue EC_{50} (μM)
431	n/a
432	n/a
433	0.00213
434	0.0015
435	0.00294
436	n/a
437	n/a
438	n/a
439	0.00392
440	0.015
441	n/a
442	0.00116
443	0.0025
444	n/a
445	n/a
446	n/a
447	n/a
448	n/a
449	n/a
450	0.000846
451	n/a
452	n/a
453	0.00181
454	0.00434
455	n/a
456	n/a
457	n/a
458	n/a
459	n/a
460	n/a
461	n/a
462	n/a
463	n/a
464	0.000659
465	0.00122
466	n/a
467	n/a
468	n/a
469	n/a

Cmpd No.	APOL1 G2 Podocyte Rescue EC_{50} (μM)
470	n/a

Cmpd No.	APOL1 G2 Podocyte Rescue EC_{50} (μM)
471	n/a

Cmpd No.	APOL1 G2 Podocyte Rescue EC_{50} (μM)
472	n/a

Example B5

[1439] APOL1 G0/G1/G2 viability assay for measurement of cytotoxicity reversal by compound in trypanosomes (APOL1 G0/G1/G2 trypanosome cell rescue assay). This example shows that the compounds of the present disclosure are able to reverse cytotoxicity in trypanosomes.

[1440] APOL1 protein expression and purification. The mature from of APOL1 proteins, residues 28-398, were expressed from a pET28a vector with an N-terminal His-tag and TEV cleavage site. Proteins were expressed in Escherichia coli BL21-CodonPlus (DE3)-RIPL cells. Liter cultures of terrific broth were grown at 37°C until an OD_{600} of ~0.8 was reached and then induced with isopropyl β-D-1-thiogalactopyranoside (IPTG; final concentration of 500 μM). Afterwards, cultures were grown for 3 hours at 37°C. For protein purification, cell pellets were resuspended in lysis buffer (50 mM Tris, pH 8.5, 5 mM EDTA, 0.5 mM DTT, 0.5 mM PMSF) supplemented with a cocktail of protease inhibitors. Cells were lysed by sonication, centrifuged, and the resulting pellet was collected. The homogenized pellet was resuspended in wash buffer (50 mM Tris, pH 8.5, 0.5 M NaCl, 5 mM EDTA, 0.5 mM DTT, 0.5 mM PMSF, protease inhibitor cocktail) and collected by centrifugation. Inclusion body dissolution was then conducted as previously reported (PNAS 112(9) (2015) 2894-2899; www.pnas.org/cgi/doi/10.1073/pnas.1421953112; herein incorporated by reference in its entirety). The solubilized APOL1 protein was applied to a nickel column (HisTrap, GE Life Sciences) preequilibrated in buffer A (50 mM Tris, pH 8.5, 0.15 M NaCl, 1% zwittergent 3–14, protease inhibitor cocktail). The resin was washed with buffer B (50 mM Tris, pH 8.5, 0.15 M NaCl, 0.1% DDM) and TEV cleavage was conducted on column overnight. Afterwards, the column was washed with buffer B, followed by His-washing buffer (50 mM Tris, pH 8.5, 0.15 M NaCl, 0.1% DDM, 10 mM imidazole). The protein was then removed from the resin using His-elution buffer (50 mM Tris, pH 8.5, 0.15 M NaCl, 0.1% DDM, 250 mM imidazole). The sample was further purified by size exclusion chromatography using a Superdex 200 Increase column (GE Life

Sciences) in 50 mM Tris, pH 8.5, 0.15 M NaCl, and 0.1% DDM buffer. All APOL1 proteins (G0, G1, and G2) were generated at Viva Biotech (Shanghai) Ltd.

[1441] Modified HMI-9 media preparation (https://tryps.rockefeller.edu/trypsru2_culture_media_preparation.html; herein incorporated by reference in its entirety). Trypanosomes were cultured in modified HMI-9 media consisting of IMDM (ThermoFisher, 12440053), 10% heat-inactivated FBS (Gibco, 10082-147), 10% Serum Plus (Sigma-Aldrich, 14008C), 1x HMI-9 supplement stock, and 1% hypoxanthine stock. The 10x HMI-9 supplement stock was made by dissolving 280 mg bathocuproine disulfonic acid (Sigma-Aldrich, 146625), 1820 mg cysteine (add after bathocuproine) (Sigma-Aldrich, 30089), 1100 mg pyruvic acid (Sigma-Aldrich, 107360), 100 mg uracil (Sigma-Aldrich, U0750), 100 mg cytosine (Sigma-Aldrich, C3506) and 140 µL 2-mercaptoethanol (Sigma-Aldrich, M3148) in 1000 mL of water. The resulting solution was aliquoted and stored at -20°C. The hypoxanthine stock was made by dissolving 4 g of NaOH into 1000 mL of water. Afterwards, 13.6 g hypoxanthine (Sigma-Aldrich, H9377) was added to this mixture. The resulting solution was aliquoted and stored at -20°C.

[1442] Assay Setup. *Trypanosoma brucei* Lister 427 VSG221 (ATCC, PRA-382) cells were cultured in modified HMI-9 media. All experiments were performed in 384-well, white, solid bottom, tissue culture treated plates (Greiner, 781080). Assay ready plates were generated with duplicate 11-point compound dilution series that consisted of 2-fold stepwise dilutions (0.4% DMSO final). To each well, was added 20 µL of 2 µg/mL of APOL1 G0, G1, or G2 recombinant protein in modified HMI-9 media using a MultiDrop Combi (final APOL1 protein concentration = 1 µg/mL). Trypanosomes were counted using a hemacytometer and diluted in modified HMI-9 media to a concentration of 1.25×10^4 cell/mL. 20 µL of this trypanosome suspension was added to each well to give a total assay volume of 40 µL and a final cell count of 250 trypanosomes/well. Plates were centrifuged at 1000 rpm for 1 minute and then incubated for 20 hours (humidified, 37°C with 5% CO_2). After incubation, the plates were equilibrated at room temperature for 1 hour. Next, 20 µL of CellTiter-Glo® reagent (Promega, G7570) was added to each well. Plates were sealed and placed on an orbital shaker (500 rpm) for 5 minutes to induce cell lysis. The plates were centrifuged at 1000 rpm for 1 minute and then incubated at room temperature for an additional 10 minutes. Luminescence signal was measured on an Envision plate reader. Collaborative Drug Discovery software was utilized for graphing data.

[1443] Table 43 below provides the results from this experiment. Unless otherwise specified, EC_{50} values are reported as the geometric mean of at least 2 assay runs on separate days. Each run represents the average of a technical replicate, where each compound was assayed twice in the same plate. A superscript † symbol indicates a value from the average of a technical replicate from a single assay run, where each compound was assayed twice in the same plate. Compounds in Table 43 are referred to by the corresponding Compound Number in Table 1, which is also referred to in the synthetic examples. When one or more of the numbered compounds are identified by stereochemistry (for example, (*R*)- or (*S*)-), the specific stereoisomer for which data is provided in Table 43 may be identified by the elution order of such compound as described in the synthetic examples. Absolute stereochemistry of such compounds may be identified by methods known in the art. For Table 43 below, n/a represents "not available".

[1444] Rescue EC_{50} values reported in Table 43 below represent the half-maximal effective concentration for reversal of cell death caused by overexpression of APOL1. This example demonstrates that compounds of the present disclosure are able to reduce cell death caused by overexpression of APOL1 at sub micromolar concentration.

Table 43.

Cmpd No.	APOL1 G1 Trypanosome Rescue EC_{50} (μM)	APOL1 G2 Trypanosome Rescue EC_{50} (μM)	APOL1 G0 Trypanosome Rescue EC_{50} (μM)
1	0.293	0.0896	0.225
2	0.191	0.0563	0.192
3	0.323	0.092	0.248
4	0.171	0.0519	0.116
5	0.171	0.052	0.15
6	0.47	0.137	0.381
7	n/a	n/a	n/a
8	n/a	n/a	n/a
9	> 4.00	1.32	> 4.00
10	0.352†	0.0933	0.351†
11	n/a	n/a	n/a
12	1.95	0.494	1.93
13	> 4.00	> 4.00	> 4.00
14	0.488	0.127	0.378
15	0.342	0.124†	0.336†
16	0.312	0.11	0.267
17	0.148	0.0367	0.108

Cmpd No.	APOL1 G1 Trypanosome Rescue EC_{50} (μM)	APOL1 G2 Trypanosome Rescue EC_{50} (μM)	APOL1 G0 Trypanosome Rescue EC_{50} (μM)
18	1.54	0.234	0.69
19	n/a	n/a	n/a
20	0.949	0.263	0.798
21	n/a	n/a	n/a
22	n/a	n/a	n/a
23	0.612†	0.113†	0.321
24	0.759†	0.163†	0.513†
25	> 4.00	1.23	> 4.00
26	> 4.00	> 4.00	> 4.00
27	0.269†	0.0663†	0.201
28	n/a	n/a	n/a
29	n/a	n/a	n/a
30	n/a	n/a	n/a
31	n/a	n/a	n/a
32	n/a	n/a	n/a
33	n/a	n/a	n/a
34	n/a	n/a	n/a
35	> 4.00	> 4.00†	> 4.00†
36	> 4.00	1.71	> 4.00
37	n/a	n/a	n/a
38	n/a	n/a	n/a
39	0.206	0.053	0.156
40	n/a	n/a	n/a
41	n/a	n/a	n/a
42	1.88	0.406	1.26
43	0.0866	0.0194	0.0522
44	0.429	0.119	0.331
45	0.747	0.162	0.476
46	0.215	0.0505	0.156
47	n/a	n/a	n/a
48	n/a	n/a	n/a
49	0.304	0.109	0.213
50	0.0449	0.0102	0.03
51	n/a	n/a	n/a
52	n/a	n/a	n/a
53	0.157	0.0478	0.156
54	n/a	n/a	n/a
55	n/a	n/a	n/a
56	0.319	0.119	0.296
57	0.672	0.183	0.673

Cmpd No.	APOL1 G1 Trypanosome Rescue EC_{50} (μM)	APOL1 G2 Trypanosome Rescue EC_{50} (μM)	APOL1 G0 Trypanosome Rescue EC_{50} (μM)
58	n/a	n/a	n/a
59	n/a	n/a	n/a
60	0.228	0.066	0.189
61	n/a	n/a	n/a
62	0.39	0.12	0.407
63	0.164†	0.0409†	0.118
64	0.712	0.167	0.503
65	0.294	0.0968	0.318
66	0.322	0.0976	0.246
67	n/a	n/a	n/a
68	0.441	0.115	0.358
69	0.184†	0.0465†	0.153†
70	> 4.00†	0.918†	> 4.00†
71	1.36†	0.205†	0.814†
72	0.177	0.0457	0.128
73	n/a	n/a	n/a
74	n/a	n/a	n/a
75	0.578	0.146	0.383
76	0.126	0.0355	0.106
77	> 4.00	1.45	> 4.00
78	0.0976	0.0326	0.0952
79	0.952	0.293	0.846
80	n/a	n/a	n/a
81	n/a	n/a	n/a
82	0.344	0.113	0.254
83	n/a	n/a	n/a
84	0.144	0.05	0.101
85	0.19	0.0485	0.115
86	0.137	0.0384	0.0964
87	0.383	0.0958	0.268
88	0.561	0.138	0.451
89	0.114	0.0327	0.101
90	0.679	0.163	0.546
91	0.0827	0.0204	0.0546
92	0.0993	0.0285	0.0844
93	0.264	0.0569	0.156
94	0.424	0.129	0.403
95	0.703	0.222	0.592
96	0.143	0.053	0.122
97	0.0984	0.0406	0.099

Cmpd No.	APOL1 G1 Trypanosome Rescue EC_{50} (μM)	APOL1 G2 Trypanosome Rescue EC_{50} (μM)	APOL1 G0 Trypanosome Rescue EC_{50} (μM)
98	0.259	0.0722	0.207
99	0.346	0.0901	0.216
100	0.113	0.0259	0.0635
101	0.2	0.0694	0.195
102	0.0505	0.018	0.0473
103	0.17	0.0437	0.113
104	0.726	0.184	0.583
105	0.274	0.0752	0.217
106	0.0918	0.0234	0.069
107	0.0935	0.023	0.0572
108	0.0307	0.00922	0.0233
109	0.385	0.098	0.32
110	0.0877	0.0261	0.0714
111	0.362	0.105	0.282
112	0.0696	0.0183	0.0582
113	0.154	0.0467	0.124
114	0.104	0.038	0.108
115	n/a	n/a	n/a
116	0.209	0.0692	0.149
117	0.423	0.117	0.309
118	n/a	n/a	n/a
119	n/a	n/a	n/a
120	1.25	0.346	0.807
121	n/a	n/a	n/a
122	0.337	0.108	0.252
123	0.258	0.0769	0.178
124	n/a	n/a	n/a
125	n/a	n/a	n/a
126	n/a	n/a	n/a
127	0.0839	0.0294	0.0649
128	0.383	0.133	0.269
129	0.0695	0.0222	0.0652
130	n/a	n/a	n/a
131	0.176	0.0478	0.132
132	0.731	0.18	0.525
133	n/a	n/a	n/a
134	0.991	0.277	0.851
135	1.2	0.303	1.08
136	0.0371	0.0143	0.0315
137	0.454	0.119	0.322

Cmpd No.	APOL1 G1 Trypanosome Rescue EC_{50} (μM)	APOL1 G2 Trypanosome Rescue EC_{50} (μM)	APOL1 G0 Trypanosome Rescue EC_{50} (μM)
138	0.585	0.165	0.326
139	0.537	0.147	0.335
140	0.653	0.164	0.408
141	n/a	n/a	n/a
142	0.0983	0.0353	0.0635
143	0.0641	0.0211	0.0411
144	0.358	0.101	0.224
145	0.118	0.0355	0.0865
146	0.427	0.119	0.346
147	0.231	0.0654	0.155
148	0.201	0.0618	0.14
149	0.174	0.0518	0.117
150	2.29	0.519	1.44
151	1.33	0.347	1.04
152	1.53	0.416	1.05
153	0.0667	0.0256	0.0522
154	0.569	0.16	0.328
155	0.0361	0.00965	0.0259
156	0.154	0.0448	0.0966
157	0.142	0.0451	0.109
158	0.142	0.0459	0.0942
159	n/a	n/a	n/a
160	0.156	0.0423	0.109
161	0.107	0.0333	0.0763
162	0.142	0.0509	0.143
163	0.09	0.0212	0.0559
164	0.349	0.0871	0.211
165	0.0338	0.0111	0.0287
166	0.112	0.0338	0.094
167	0.148	0.035	0.0984
168	0.638	0.191	0.496
169	0.918	0.295	0.619
170	n/a	n/a	n/a
171	n/a	n/a	n/a
172	0.353	0.108	0.246
173	n/a	n/a	n/a
174	0.481	0.137	0.401
175	n/a	n/a	n/a
176	0.177	0.0446	0.12
177	0.314	0.0844	0.26

Cmpd No.	APOL1 G1 Trypanosome Rescue EC_{50} (μM)	APOL1 G2 Trypanosome Rescue EC_{50} (μM)	APOL1 G0 Trypanosome Rescue EC_{50} (μM)
178	n/a	n/a	n/a
179	n/a	n/a	n/a
180	0.0477	0.0133	0.0352
181	0.232	0.0707	0.158
182	0.481	0.138	0.401
183	n/a	n/a	n/a
184	2.08	0.585	1.6
185	0.479	0.14	0.31
186	n/a	n/a	n/a
187	n/a	n/a	n/a
188	0.0965	0.0267	0.071
189	0.246	0.0614	0.167
190	0.104	0.0357	0.0921
191	0.304	0.104	0.251
192	0.142	0.0491	0.108
193	0.288	0.0702	0.2
194	n/a	n/a	n/a
195	0.0744	0.0198	0.0482
196	0.185	0.0603	0.16
197	0.193	0.0106	0.0303
198	0.142	0.0419	0.107
199	n/a	n/a	n/a
200	0.192	0.0724	0.185
201	n/a	n/a	n/a
202	n/a	n/a	n/a
203	0.583	0.227	0.565
204	n/a	n/a	n/a
205	n/a	n/a	n/a
206	n/a	n/a	n/a
207	n/a	n/a	n/a
208	n/a	n/a	n/a
209	n/a	n/a	n/a
210	0.0711	0.0218	0.0638
211	0.527	0.159	0.48
212	0.103	0.0321	0.0696
213	n/a	n/a	n/a
214	0.43	0.0887	0.25
215	0.097	0.0224	0.0701
216	0.912	0.231	0.629
217	n/a	n/a	n/a

Cmpd No.	APOL1 G1 Trypanosome Rescue EC_{50} (μM)	APOL1 G2 Trypanosome Rescue EC_{50} (μM)	APOL1 G0 Trypanosome Rescue EC_{50} (μM)
218	0.108	0.0316	0.0651
219	0.039	0.0105	0.0223
220	n/a	n/a	n/a
221	0.129	0.0295	0.075
222	n/a	n/a	n/a
223	n/a	n/a	n/a
224	0.0928	0.0327	0.066
225	0.0508	0.0129	0.0352
226	0.112	0.036	0.08
227	0.248	0.0616	0.142
228	0.363	0.0862	0.196
229	0.778	0.186	0.417
230	0.801	0.209	0.427
231	0.231	0.0667	0.135
232	0.157	0.0416	0.0976
233	0.134	0.0411	0.0817
234	0.475	0.146	0.272
235	0.452	0.132	0.27
236	0.866	0.397	0.766
237	0.196	0.0572	0.132
238	> 4.00	0.763	1.59
239	0.0488	0.0148	0.04
240	n/a	n/a	n/a
241	0.258	0.0633	0.177
242	n/a	n/a	n/a
243	n/a	n/a	n/a
244	0.151	0.0493	0.141
245	0.379	0.102	0.265
246	n/a	n/a	n/a
247	0.246	0.081	0.186
248	0.126	0.0379	0.0862
249	0.0738	0.0221	0.0538
250	0.678	0.194	0.445
251	1.12	0.24	0.903
252	n/a	n/a	n/a
253	n/a	n/a	n/a
254	0.951	0.252	0.695
255	2.92	0.575	1.38
256	n/a	n/a	n/a
257	n/a	n/a	n/a

Cmpd No.	APOL1 G1 Trypanosome Rescue EC_{50} (μM)	APOL1 G2 Trypanosome Rescue EC_{50} (μM)	APOL1 G0 Trypanosome Rescue EC_{50} (μM)
258	n/a	n/a	n/a
259	0.0922	0.0255	0.068
260	0.397	0.11	0.274
261	0.1	0.0296	0.084
262	n/a	n/a	n/a
263	0.32	0.0953	0.226
264	n/a	n/a	n/a
265	0.105	0.0231	0.0676
266	0.407	0.0771	0.236
267	0.115	0.0337	0.0954
268	0.121	0.0327	0.108
269	0.277	0.0797	0.207
270	0.0822	0.0253	0.0725
271	0.0507	0.0159	0.051
272	0.0732	0.0189	0.0589
273	0.0716	0.0258	0.0649
274	0.0584	0.0172	0.0593
275	0.0736	0.0214	0.0612
276	0.185	0.055	0.178
277	n/a	n/a	n/a
278	0.111	0.0255	0.114
279	0.283	0.0831	0.213
280	n/a	n/a	n/a
281	0.101	0.0281	0.0959
282	0.23	0.0598	0.181
283	0.235	0.0711	0.216
284	0.943	0.235	0.808
285	0.749	0.212	0.547
286	0.629	0.175	0.505
287	0.05†	0.0139†	0.0376†
288	0.0361†	0.00975†	0.0262†
289	0.0519	0.0157	0.0382
290	0.0692	0.024	0.0555
291	0.0797	0.0265	0.0631
292	0.0396	0.0108	0.0316
293	n/a	n/a	n/a
294	0.089	0.0214	0.0619
295	0.0402	0.0111	0.0326
296	n/a	n/a	n/a
297	0.0854	0.0315	0.0726

Cmpd No.	APOL1 G1 Trypanosome Rescue EC_{50} (μM)	APOL1 G2 Trypanosome Rescue EC_{50} (μM)	APOL1 G0 Trypanosome Rescue EC_{50} (μM)
298	0.156	0.0566	0.119
299	n/a	n/a	n/a
300	0.543	0.16	0.375
301	0.447	0.134	0.327
302	0.498	0.142	0.356
303	n/a	n/a	n/a
304	n/a	n/a	n/a
305	0.265	0.0804	0.187
306	0.0508	0.015	0.037
307	0.0797	0.0272	0.0657
308	0.435	0.15	0.335
309	0.0706	0.0234	0.0582
310	n/a	n/a	n/a
311	0.0503	0.0138	0.0374
312	0.0344	0.0101	0.0282
313	0.0718	0.0202	0.0545
314	0.0349	0.0115	0.0254
315	n/a	n/a	n/a
316	n/a	n/a	n/a
317	0.0335	0.0115	0.033
318	n/a	n/a	n/a
319	0.0811	0.027	0.0697
320	n/a	n/a	n/a
321	0.0459	0.0143	0.0396
322	0.0349	0.0117	0.0293
323	0.0359	0.0118	0.032
324	0.035	0.00831	0.0289
325	0.269	0.0775	0.213
326	0.0944	0.0327	0.0886
327	0.0466	0.0134	0.0399
328	0.0921	0.0239	0.0799
329	0.24	0.0673	0.199
330	n/a	n/a	n/a
331	n/a	n/a	n/a
332	n/a	n/a	n/a
333	0.205†	0.074†	0.152†
334	n/a	n/a	n/a
335	n/a	n/a	n/a
336	n/a	n/a	n/a
338	n/a	n/a	n/a

Cmpd No.	APOL1 G1 Trypanosome Rescue EC_{50} (μM)	APOL1 G2 Trypanosome Rescue EC_{50} (μM)	APOL1 G0 Trypanosome Rescue EC_{50} (μM)
339	n/a	n/a	n/a
340	n/a	n/a	n/a
341	n/a	n/a	n/a
342	n/a	n/a	n/a
343	0.203†	0.0642†	0.174†
344	n/a	n/a	n/a
345	0.242†	0.0802†	0.161†
346	0.116†	0.0377†	0.0836†
347	n/a	n/a	n/a
348	n/a	n/a	n/a
349	0.0898†	0.0331†	0.0646†
350	n/a	n/a	n/a
351	n/a	n/a	n/a
352	0.0188	0.00822	0.0187
353	n/a	n/a	n/a
354	n/a	n/a	n/a
355	n/a	n/a	n/a
356	0.113†	0.0374†	0.101†
357	0.0916	0.0281	0.0612
358	0.0752	0.0313	0.0621
359	n/a	n/a	n/a
360	n/a	n/a	n/a
361	n/a	n/a	n/a
362	n/a	n/a	n/a
363	n/a	n/a	n/a
364	0.203	0.0923	0.155
365	n/a	n/a	n/a
366	0.0873	0.0324	0.0664
367	0.323	0.106	0.231
368	n/a	n/a	n/a
369	n/a	n/a	n/a
370	n/a	n/a	n/a
371	0.0219	0.00916	0.0188
372	n/a	n/a	n/a
373	n/a	n/a	n/a
374	n/a	n/a	n/a
375	n/a	n/a	n/a
376	0.115†	0.0399†	0.0956†
377	0.271†	0.0978†	0.205†
378	n/a	n/a	n/a

Cmpd No.	APOL1 G1 Trypanosome Rescue EC_{50} (μM)	APOL1 G2 Trypanosome Rescue EC_{50} (μM)	APOL1 G0 Trypanosome Rescue EC_{50} (μM)
379	n/a	n/a	n/a
380	n/a	n/a	n/a
381	n/a	n/a	n/a
382	n/a	n/a	n/a
383	n/a	n/a	n/a
384	n/a	n/a	n/a
385	n/a	n/a	n/a
386	n/a	n/a	n/a
387	n/a	n/a	n/a
388	n/a	n/a	n/a
389	n/a	n/a	n/a
390	n/a	n/a	n/a
391	n/a	n/a	n/a
392	0.0794†	0.0285†	0.07†
393	0.36†	0.12†	0.3†
394	n/a	n/a	n/a
395	0.312	0.106	0.24
396	n/a	n/a	n/a
397	0.269	0.0852	0.226
398	0.0522	0.018	0.0536
399	n/a	n/a	n/a
400	n/a	n/a	n/a
401	n/a	n/a	n/a
402	0.0427	0.0165	0.0336
403	n/a	n/a	n/a
404	0.554	0.21	0.425
405	0.0216	0.00806	0.02
406	0.128	0.0511	0.107
407	0.0997†	0.033†	0.0724
408	0.121	0.0436	0.0848†
409	n/a	n/a	n/a
410	0.269	0.0924	0.206
411	n/a	n/a	n/a
412	n/a	n/a	n/a
413	n/a	n/a	n/a
414	n/a	n/a	n/a
415	n/a	n/a	n/a
416	n/a	n/a	n/a
417	n/a	n/a	n/a
418	n/a	n/a	n/a

Cmpd No.	APOL1 G1 Trypanosome Rescue EC_{50} (μM)	APOL1 G2 Trypanosome Rescue EC_{50} (μM)	APOL1 G0 Trypanosome Rescue EC_{50} (μM)
419	n/a	n/a	n/a
420	n/a	n/a	n/a
421	n/a	n/a	n/a
422	n/a	n/a	n/a
423	n/a	n/a	n/a
424	n/a	n/a	n/a
425	n/a	n/a	n/a
426	0.0888	0.0367	0.071
427	0.0181	0.00662	0.0156
428	0.0719	0.0323	0.0633
429	n/a	n/a	n/a
430	n/a	n/a	n/a
431	n/a	n/a	n/a
432	n/a	n/a	n/a
433	n/a	n/a	n/a
434	n/a	n/a	n/a
435	0.0272†	0.0145†	0.0271†
436	n/a	n/a	n/a
437	n/a	n/a	n/a
438	n/a	n/a	n/a
439	0.051†	0.0202†	0.0505†
440	0.205	0.0705	0.16
441	0.215	0.0783	0.144
442	n/a	n/a	n/a
443	n/a	n/a	n/a
444	n/a	n/a	n/a
445	n/a	n/a	n/a
446	n/a	n/a	n/a
447	n/a	n/a	n/a
448	n/a	n/a	n/a
449	n/a	n/a	n/a
450	n/a	n/a	n/a
451	n/a	n/a	n/a
452	n/a	n/a	n/a
453	n/a	n/a	n/a
454	n/a	n/a	n/a
455	n/a	n/a	n/a
456	n/a	n/a	n/a
457	n/a	n/a	n/a
458	n/a	n/a	n/a

Cmpd No.	APOL1 G1 Trypanosome Rescue EC_{50} (μM)	APOL1 G2 Trypanosome Rescue EC_{50} (μM)	APOL1 G0 Trypanosome Rescue EC_{50} (μM)
459	0.133	0.0498	0.101
460	0.118	0.0537	0.104
461	0.0755†	0.0288†	0.0692†
462	n/a	n/a	n/a
463	n/a	n/a	n/a
464	n/a	n/a	n/a
465	n/a	n/a	n/a
466	0.0306	0.0119	0.0194
467	0.00603	0.00224	0.00374
468	0.00559	0.0024	0.00372
469	0.0155	0.00533	0.00976
470	0.0124	0.00441	0.00882
471	n/a	n/a	n/a
472	n/a	n/a	n/a

Example B6

[1445] APOL1 G2 mouse renal model for measurement of albuminuria prevention by compound. This example shows that the compounds of the present disclosure are able to prevent albuminuria.

[1446] APOL1 transgenic (Tg) mice with a bacterial artificial chromosome (BAC) containing APOL1 G2 and its upstream and downstream genomic regions (Taconic, Model # 13022) were bred to homozygosity. APOL1 G2 homozygous (G2 HOM) male mice, greater than 6 weeks of age were utilized in experiments. All studies were conducted under a protocol approved by the Institutional Animal Care and Use Committee (IACUC).

[1447] Baseline urine samples were collected over a 24-hour period 7 days prior to the start of the experiment. Urine volume was determined by weight and stored at -80°C until use. Afterwards, baseline blood samples were collected via submandibular bleed into serum separate (SS) tubes (BD Microtainer). Serum samples were allowed to clot at room temperature for 30 minutes prior to centrifugation at 12000 rpm, 4°C for 5 minutes. The concentration of APOL1 was determined in these samples using an APOL1 ELISA kit (Proteintech, KE00047) according to the manufacturer's instructions.

[1448] On the day of the experiment (0 hour), mice were individually identified, weighed, and assigned to one of the treatment groups. Treatment groups had similar average levels of serum APOL1. Mice were administered with two doses of compound test article and one dose of recombinant mouse interferon gamma (mIFNγ) (MilliporeSigma, Catalog #IF005) per day for 2 days. Compound test article was administered via oral gavage at 10 mL/kg body weight dose volume at 0, approximately 10, 24, and 34 hours. mIFNγ (1.5×10^{11} unit/kg body weight) was administered via intraperitoneal injection at 10 mL/kg body weigh dose volume at 0 and 24 hours. Urine collection was immediately initiated after the second dose of mIFNγ. Specifically, mice were individually placed in a metabolic cage (Lab Products) for 24 hours where urine and feces were collected into separate tubes. During this time, mice had access to an enrichment toy, gel diet (Bio-serve), and drinking water (Innovive). At the end of the experiment, mice were anesthetized under isoflurane and blood was collected via cardiac puncture followed with a cervical dislocation to ensure death.

[1449] Urine samples were analyzed for urine albumin and urine creatinine levels. The concentration of urine albumin was determined using a mouse albumin immunoperoxidase assay kit (Immunology Consultants Laboratory, E-90AL) according to the manufacturer's instructions. Urine creatinine was analyzed using LC-MS methodology at WuXi App Tec (DMPK, New Jersey, USA).

[1450] Selected compounds from Table 1 described by formula (I-E) were tested in this APOL1 G2 mouse renal model for measurement of albuminuria. The results are shown in Table 44.

Table 44.

Compound Tested	Dose (route of administration)	Reduction in urine albumin/creatinine ratio (uACR)
Compound A	0.3 mg/kg (PO, BID)	50%
Compound A	1 mg/kg (PO, BID)	58%
Compound A	3 mg/kg (PO, BID)	75%
Compound B	10 mg/kg (PO, BID)	67%
Compound B	50 mg/kg (PO, BID)	89%

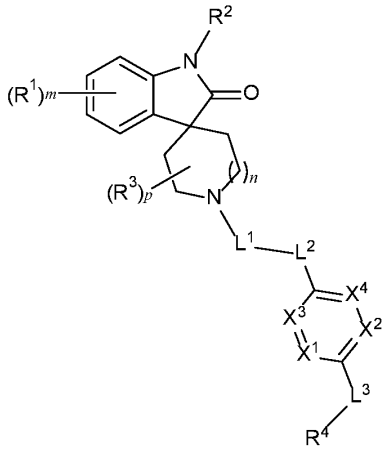
[1451] All publications, patent applications, patents, and other references mentioned herein are expressly incorporated by reference in their entireties, to the same extent as if each were incorporated by reference individually.

[1452] It is to be understood that, while the disclosure has been described in conjunction with the above embodiments, the foregoing description and examples are intended to illustrate and not limit the scope of the disclosure. Other aspects, advantages and modifications within the scope of the disclosure will be apparent to those skilled in the art to which the disclosure pertains.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of formula (II):



(II),

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

m is an integer from 0 to 4;

n is an integer from 0 to 2;

p is an integer from 0 to 10;

R^1, if present is, independently at each occurrence selected from the group consisting of halo, -CN, C_{1-6}alkoxy, and C_{1-6}alkyl, wherein

the C_{1-6}alkoxy of R^1 is optionally substituted with one or more halo, and

the C_{1-6}alkyl of R^1 is optionally substituted with one or more halo;

R^2 is H, C_{1-6}alkyl, C_{3-10}cycloalkyl, or 3-15 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^2 is optionally substituted with one or more deuterium, halo, -OH, $-NH_2$, or C_{1-6}alkoxy, and

the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more -OH;

R^3, if present, is C_{1-6}alkyl;

L^1 is C_{1-6}alkylene, wherein

the C_{1-6}alkylene of L^1 is optionally substituted with one or more deuterium or C_{1-6}alkyl, and wherein

the C_{1-6}alkyl is further optionally substituted with one or more -OH or C_{1-6}alkoxy;

L^2 is O or $N(R^x)$, wherein R^x is H or C_{1-6}alkyl; and

either

(1) L^3 is absent or is O, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or C_{1-6}alkylene, wherein

the C_{3-10}cycloalkyl of L^3 is optionally substituted with one or more –OH or C_{1-6}alkyl,

the C_{1-6}alkylene of L^3 is optionally substituted with one or more –OH or C_{1-6}alkyl, wherein

the C_{1-6}alkyl is optionally substituted with one or more -OH, and

the 3-10 membered heterocyclyl of L^3 is optionally substituted with one or more –OH or C_{1-6}alkyl;

X^1 and X^2 are each independently N or $C(R^5)$; and

R^4 is:

(i) $-S(O)_2-R^a$;

(ii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^4 is optionally substituted with one or more C_{1-6}alkyl;

(iii) $-N(R^d)_2$, wherein R^d is independently at each occurrence H, C_{1-6} alkyl, or $-S(O)_2-R^a$, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more -OH,

(iv) $-NS(O)-(C_{1-6}alkyl)_2$, wherein the C_{1-6}alkyl is optionally substituted with one or more –OH,

(v) $-C(O)-N(R^e)_2$ wherein R^e is independently at each occurrence H, C_{1-6} alkyl, or 3-10 membered heterocycle, wherein

the 3-10 membered heterocycle of R^e is optionally substituted with one or more oxo, or both R^e together with the N to which they are attached are taken together to form a 3-10 membered heterocyclyl, wherein

the 3-10 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, $-NH-S(O)_2-R^a$, or $-S(O)_2-R^a$,

(vi) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl, -OH , oxo or $-S(O)_2R^a$,

(vii) $-S(O)-N(C_{1-6}alkyl)-(C_{1-6}alkyl)$,

(viii) -CN,

(ix) $-(CH_2)_qOH$, wherein q is an integer from 0-6,

(x) $-C(O)-C_{1-6}$alkyl, or

(xi) $-P(O)(C_{1-6}alkyl)_2$;

or

(2) L^3 is absent; and

one of X^1 and X^2 is N or $C(R^5)$; and

the other of X^1 and X^2 is N or C that is taken together with R^4, and the atoms to which they are attached, to form a 5-10 membered heterocyclyl or a 5-20 membered heteroaryl, wherein

the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein

R^b is, independently at each occurrence, selected from the group consisting of -OH, halo, oxo, C_{1-6}alkyl, $-C(O)-C_{1-6}$alkyl, $-C(O)-NH_2$, $-C(O)-NH(C_{1-6}alkyl)$, $-C(O)-N(C_{1-6}alkyl)_2$, $-S(O)_2-R^a$, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, OH, $-S(O)_2-C_{1-6}$alkyl, or C_{3-10}cycloalkyl, and wherein

the C_{3-10}cycloalkyl of the C_{1-6}alkyl of R^b is further optionally substituted with one or more C_{1-6}alkyl or -OH and

the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more -OH, C_{3-10}cycloalkyl, or C_{1-6}alkyl, and wherein

the C_{1-6}alkyl of the C_{3-10}cycloalkyl of R^b is further optionally substituted with one or more -OH, deuterium, or halo, and

the 5-20 membered heteroaryl is optionally substituted with one or more R^c, wherein

R^c is, independently at each occurrence, selected from the group consisting of halo, C_{1-6}alkyl, $-C(O)-C_{1-6}$alkyl, $-C(O)-NH_2$, $-C(O)-NH(C_{1-6}alkyl)$, $-C(O)-N(C_{1-6}alkyl)_2$, $-S(O)_2-R^a$, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more $-S(O)_2-C_{1-6}$alkyl,

the C_{3-10}cycloalkyl of R^c is optionally substituted with one or more -OH or C_{1-6}alkyl, and

the 3-10 membered heterocyclyl of R^c is optionally substituted with one or more -OH or C_{1-6}alkyl, and wherein

the C_{1-6}alkyl of the 3-10 membered heterocyclyl of R^c is further optionally substituted with one or more -OH;

R^a is, independently at each occurrence:

(i) C_{1-6}alkyl optionally substituted with one or more halo, -OH, -$S(O)_2$-C_{1-6}alkyl, or -N(C_{1-6}alkyl)-C(O)-C_{1-6}alkyl,

(ii) C_{3-10}cycloalkyl optionally substituted with one or more -OH, -$C(O)_2$-C_{1-6}alkyl, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, or –C(O)-C_{3-10}heterocyclyl, or C_{1-6}alkyl, wherein

the C_{1-6}alkyl is optionally substituted with one or more -OH,

(iii) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl, or

(iv) NH(C_{1-6}alkyl);

R^5 is, independently at each occurrence, H, halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein

the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo or -OH, and

the C_{1-6}alkoxy of R^5 is optionally substituted with one or more halo;

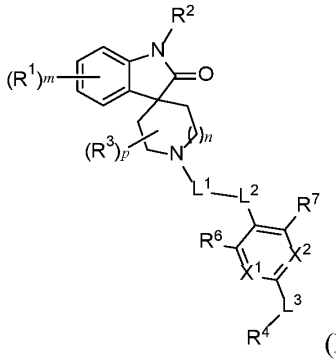
X^3 is N or C(R^6);

X^4 is N or C(R^7);

and

R^6 and R^7 are each independently H or halo.

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



(I'),

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

m is an integer from 0 to 4;

n is an integer from 0 to 2;

p is an integer from 0 to 10;

R^1, if present is, independently at each occurrence selected from the group consisting of halo, -CN, C_{1-6}alkoxy, or C_{1-6}alkyl, wherein

the C_{1-6}alkoxy of R^1 is optionally substituted with one or more halo, and

the C_{1-6}alkyl of R^1 is optionally substituted with one or more halo;

R^2 is H, C_{1-6}alkyl, C_{3-10}cycloalkyl, or 3-15 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^2 is optionally substituted with one or more halo, -OH, $-NH_2$, or C_{1-6}alkoxy, and

the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more -OH;

R^3, if present, is C_{1-6}alkyl;

L^1 is C_{1-6}alkylene, wherein the C_{1-6}alkylene of L^1 is optionally substituted with one or more C_{1-6}alkyl, and wherein the C_{1-6}alkyl is further optionally substituted with one or more -OH or C_{1-6}alkoxy;

L^2 is O or $N(R^x)$, wherein R^x is H or C_{1-6}alkyl; and

either

(1) L^3 is absent or is O, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or C_{1-6}alkylene, wherein

the C_{3-10}cycloalkyl is optionally substituted with one or more –OH, or C_{1-6}alkyl,

the C_{1-6}alkylene of L^3 is optionally substituted with one or more –OH, or C_{1-6}alkyl, and

the 3-10 membered heterocyclyl is optionally substituted with one or more –OH;

X^1 and X^2 are each independently N or $C(R^5)$; and

R^4 is:

(i) $-S(O)_2-R^a$;

(ii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^4 is optionally substituted with one or more C_{1-6}alkyl;

(iii) $-N(R^d)_2$, wherein R^d is independently at each occurrence H, C_{1-6} alkyl, or $-S(O)_2-R^a$, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more –OH,

(iv) $-NS(O)-(C_{1-6}alkyl)_2$, wherein the C_{1-6}alkyl is optionally substituted with one or more –OH,

(v) $-C(O)-N(R^e)_2$ wherein R^e is independently at each occurrence H, C_{1-6} alkyl, or 3-10 membered heterocycle, wherein the 3-10 membered heterocycle is optionally

substituted with one or more oxo, or both R^e together with the N to which they are attached are taken together to form a 3-10 membered heterocyclyl, wherein the 3-10 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, -NH-$S(O)_2$-R^a, or -$S(O)_2$-R^a,

(vi) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl, -OH , oxo or -$S(O)_2R^a$,

(vii) -S(O)-N(C_{1-6}alkyl)-(C_{1-6}alkyl),

(viii) -CN,

(ix) -$(CH_2)_q$OH, wherein q is an integer from 0-6,

(x) -C(O)-C_{1-6}alkyl, or

(xi) -P(O)(C_{1-6}alkyl)$_2$;

or

(2) L^3 is absent; and

one of X^1 and X^2 is N or C(R^5); and

the other of X^1 and X^2 is N or C that is taken together with R^4, and the atoms to which they are attached, to form a 5-10 membered heterocyclyl or a 5-20 membered heteroaryl, wherein

the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is, independently at each occurrence, selected from the group consisting of halo, oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -$S(O)_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, OH, -$S(O)_2$-C_{1-6}alkyl, or C_{3-10}cycloalkyl, and

wherein the C_{3-10}cycloalkyl of the C_{1-6}alkyl of R^b is further optionally substituted with one or more C_{1-6}alkyl or -OH and

the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more -OH, C_{3-10}cycloalkyl, or C_{1-6}alkyl, and

wherein the C_{1-6}alkyl of the C_{3-10}cycloalkyl of R^b is further optionally substituted with one or more –OH, and

the 5-20 membered heteroaryl is optionally substituted with one or more R^c, wherein R^c is, independently at each occurrence, selected from the group consisting of halo, C_{1-6}alkyl,

-C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -S(O)$_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more -S(O)$_2$-C_{1-6}alkyl,

the C_{3-10}cycloalkyl of R^c is optionally substituted with one or more –OH, or C_{1-6}alkyl,

and the 3-10 membered heterocyclyl of R^c is optionally substituted with one or more -OH, or C_{1-6}alkyl, and

wherein the C_{1-6}alkyl of 3-10 membered heterocyclyl of R^c is further optionally substituted with one or more -OH;

R^a is, independently at each occurrence:

(i) C_{1-6}alkyl optionally substituted with one or more halo, -OH, -S(O)$_2$-C_{1-6}alkyl, or -N(C_{1-6}alkyl)-C(O)-C_{1-6}alkyl,

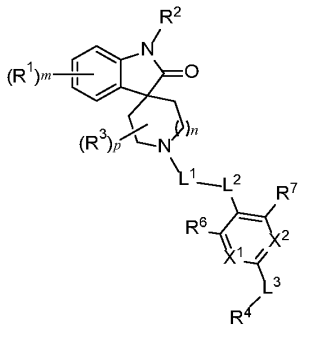
(ii) C_{3-10}cycloalkyl optionally substituted with one or more -OH, -C(O)$_2$-C_{1-6}alkyl, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, or –C(O)-C_{3-10}heterocyclyl, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more -OH, or

(iii) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl;

R^5 is, independently at each occurrence, H, halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH and wherein the C_{1-6}alkoxy of R^5 is optionally substituted with one or more halo; and

R^6 and R^7 are each independently H or halo.

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



(I),

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

either

(1) L^3 is absent or is O, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or C_{1-6}alkylene, wherein the C_{1-6}alkylene of L^3 is optionally substituted with one or more C_{1-6}alkyl, and the 3-10 membered heterocyclyl is optionally substituted with one or more –OH;

X^1 and X^2 are each independently N or $C(R^5)$; and

R^4 is:

(i) $-S(O)_2-R^a$;

(ii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^4 is optionally substituted with one or more C_{1-6}alkyl;

(iii) $-N(R^d)_2$, wherein R^d is independently at each occurrence H, C_{1-6} alkyl, or $-S(O)_2-R^a$, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more –OH,

(iv) $-NS(O)-(C_{1-6}alkyl)_2$, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more –OH,

(v) $-C(O)-N(R^e)_2$ wherein R^e is independently at each occurrence H, C_{1-6} alkyl, or 3-10 membered heterocycle, wherein the 3-10 membered heterocycle is optionally substituted with one or more oxo, or both R^e together with the N to which they are attached are taken together to form a 3-10 membered heterocyclyl, wherein the 3-10 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, $NH-S(O)_2-R^a$, or $-S(O)_2-R^a$,

(vi) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl or oxo,

(vii) -S(O)-N(C_{1-6}alkyl)-(C_{1-6}alkyl),

(viii) –CN; or

or

(2) L^3 is absent; and

one of X^1 and X^2 is N or C(R^5); and

the other of X^1 and X^2 is N or C that is taken together with R^4, and the atoms to which they are attached, to form a 5-10 membered heterocyclyl or a 5-20 membered heteroaryl, wherein

the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein R^b is, independently at each occurrence, selected from the group consisting of halo, oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -S(O)$_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, OH, or -S(O)$_2$-C_{1-6}alkyl, and

the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more -OH, and

the 5-20 membered heteroaryl is optionally substituted with one or more R^c, wherein R^c is, independently at each occurrence, selected from the group consisting of halo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -S(O)$_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more -S(O)$_2$-C_{1-6}alkyl, and

the C_{3-10}cycloalkyl of R^c is optionally substituted with one or more -OH;

R^a is, independently at each occurrence:

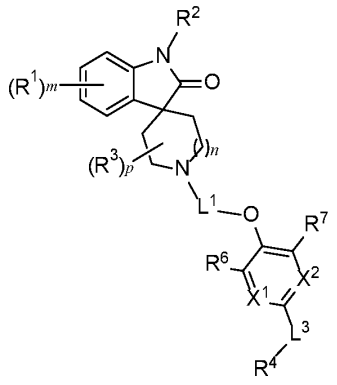
(i) C_{1-6}alkyl optionally substituted with one or more halo, -OH, -S(O)$_2$-C_{1-6}alkyl, or -N(C_{1-6}alkyl)-C(O)-C_{1-6}alkyl, or

(ii) C_{3-10}cycloalkyl optionally substituted with one or more -OH, -C(O)$_2$-C_{1-6}alkyl, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, or –C(O)-C_{3-10}heterocyclyl, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more -OH, or

(iii) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl;

R^5 is, independently at each occurrence, H, halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, or -OH and wherein the C_{1-6}alkoxy is optionally substituted with one or more halo; and
R^6 and R^7 are each independently H or halo.

4. The compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein L^2 is -O-, such that the compound is a compound of formula (I-A):



(I-A),

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

5. The compound of any one of claims 1-4, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein *n* is 1, or 2.

6. The compound of any one of claims 1-5, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is H, C_{1-3}alkyl, C_{3-6}cycloalkyl, or 3-10 membered heterocyclyl, wherein the C_{1-3}alkyl of R^2 is optionally substituted with one or more deuterium, halo, -OH, $-NH_2$, or C_{1-3}alkoxy, and the C_{3-6}cycloalkyl of R^2 is optionally substituted with one or more -OH.

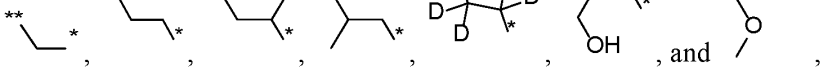
7. The compound of any one of claims 1-6, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein *m* is 0, 1, or 2.

8. The compound of any one of claims 1-7 or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is halo, -CN, or -C_{1-3}alkyl, wherein the C_{1-3}alkyl of R^1 is optionally substituted with one or more halo.

9. The compound of any one of claims 1-8, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein *p* is 0 or 1.

10. The compound of any one of claims 1-9, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^3 is C_{1-6}alkyl.

11. The compound of any one of claims 1-10, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein L^1 is C_{1-3}alkylene, wherein the C_{1-3}alkylene of L^1 is optionally substituted with one or more deuterieum or C_{1-3}alkyl, wherein the C_{1-3}alkyl is optionally substituted with -OH or C_{1-3}alkoxy.

12. The compound of any one of claims 1-11, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein L^1 is selected from the group consisting of  , wherein, for each L^1, * denotes the point of attachment to L^2 and ** denotes the point of attachment to the remainder of the molecule.

13. The compound of any one of claims 1-12, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein L^2 is O.

14. The compound of any one of claims 1-13, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein L^3 is absent.

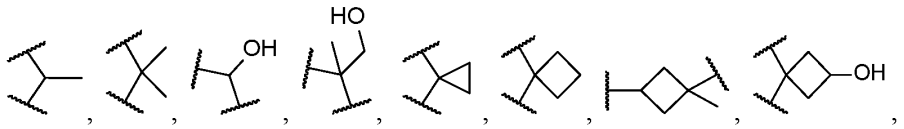
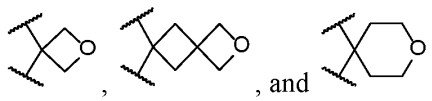
15. The compound of any one of claims 1-13, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein L^3 is -O-, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or C_{1-6}alkylene, wherein

the C_{3-10}cycloalkyl of L^3 is optionally substituted with one or more –OH or C_{1-6}alkyl,

the C_{1-6}alkylene of L^3 is optionally substituted with one or more –OH or C_{1-6}alkyl, wherein

the C_{1-6}alkyl is optionally substituted with one or more -OH, and

the 3-10 membered heterocyclyl of L^3 is optionally substituted with one or more –OH or C_{1-6}alkyl.

16. The compound of any one of claims 1-13, and 15 or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein L^3 is selected from the group consisting of -O-,  ,  , and .

17. The compound of any one of claims 1-16 or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^4 is $S(O)_2$-R^a, 5-10 membered heteroaryl, -N(R^d)$_2$, -NS(O)-(C_{1-3}alkyl)$_2$, -C(O)-N(R^e)$_2$, 3-6 membered heterocyclyl, -S(O)(N-C_{1-3}alkyl)-(C_{1-3}alkyl), –CN, -OH, -C(O)-C_{1-3}alkyl, or -P(O)(C_{1-3}alkyl)$_2$, wherein

the 5-20 membered heteroaryl of R^4 is optionally substituted with one or more C_{1-3}alkyl, and

the 3-6 membered heterocyclyl optionally substituted with one or more -OH, oxo, C_{1-3}alkyl, or -$S(O)_2$-R^a.

18. The compound of claim 17 or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^a is C_{1-6}alkyl, C_{3-10}cycloalkyl, or 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^a is optionally substituted with one or more halo, -OH, -$S(O)_2$-C_{1-6}alkyl, or -N(C_{1-6}alkyl)-C(O)-C_{1-6}alkyl,

the C_{3-10}cycloalkyl of R^a is optionally substituted with one or more -OH, $C(O)_2$-C_{1-6}alkyl, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -C(O)-C_{3-10}heterocyclyl or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more –OH, and

the 3-10 membered heterocyclyl of R^a is optionally substituted with one or more C_{1-6}alkyl.

19. The compound of claim 17, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^d is independently at each occurrence H, C_{1-6} alkyl, or -$S(O)_2$-R^a, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more -OH, and wherein R^a is C_{1-6}alkyl.

20. The compound of claim 17, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^e is independently at each occurrence H, C_{1-6}alkyl, or 3-10 membered heterocycle, wherein the 3-6 membered heterocycle is optionally substituted with one or more oxo.

21. The compound of claim 17 or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein both R^e together with the N to which they are attached are taken together to form a 3-10 membered heterocyclyl, wherein the 3-10 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, -NH_2, -NH-$S(O)_2$-R^a, or -$S(O)_2$-R^a, wherein R^a is C_{1-6}alkyl.

22. The compound of any one of claims 1-21, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein each of X^1 and X^2 is C(R^5).

23. The compound of any one of claims 1-21, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein each of X^1 and X^2 is N.

24. The compound of any one of claims 1-21, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein one of X^1 and X^2 is N and the other is $C(R^5)$.

25. The compound of any one of claims 1-21, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein one of X^1 and X^2 is N or CR^5, and the other of X^1 and X^2 is N or C that is taken together with R^4, and the atoms to which they are attached, to form a 5-10 membered heterocyclyl optionally substituted with one or more of R^b.

26. The compound of claim 25, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^b is independently at each occurrence, selected from the group consisting of -OH, halo, oxo, C_{1-3}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-3}alkyl), -C(O)-N(C_{1-3}alkyl)$_2$, -$S(O)_2$-R^a, C_{3-6}cycloalkyl, and 3-6 membered heterocyclyl, wherein the C_{1-3}alkyl of R^b is optionally substituted with one or more halo, OH, -$S(O)_2$-C_{1-3}alkyl, or C_{3-6}cycloalkyl, and wherein the C_{3-6}cycloalkyl of the C_{1-3}alkyl of R^b is further optionally substituted with one or more C_{1-3}alkyl or -OH and the C_{3-6}cycloalkyl of R^b is optionally substituted with one or more -OH, C_{3-6}cycloalkyl, or C_{1-3}alkyl, and wherein the C_{1-3}alkyl of the C_{3-6}cycloalkyl of R^b is further optionally substituted with one or more -OH, deuterium, or halo.

27. The compound of any one of claims 1-21, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein one of X^1 and X^2 is N or CR^5, and the other of X^1 and X^2 is N or C that is taken together with R^4, and the atoms to which they are attached, to form a 5-10 membered heteroaryl optionally substituted with one or more R^c.

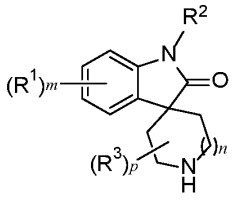
28. The compound of claim 27, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein, R^c is independently at each occurrence, selected from the group consisting of halo, C_{1-3}alkyl, -C(O)-C_{1-3}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-3}alkyl), -C(O)-N(C_{1-3}alkyl)$_2$, -$S(O)_2$-R^a, C_{3-6}cycloalkyl, and 3-6 membered heterocyclyl, wherein the C_{1-6}alkyl of R^c is optionally substituted with one or more -$S(O)_2$-C_{1-3}alkyl, the C_{3-10}cycloalkyl of R^c is optionally substituted with one or more -OH, or C_{1-3}alkyl, and the 3-6 membered heterocyclyl of R^c

is optionally substituted with one or more -OH or C_{1-3}alkyl, and wherein the C_{1-3}alkyl of the 3-6 membered heterocyclyl of R^c is further optionally substituted with one or more -OH.

29. The compound of any one of claims 1-28, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^5 is independently at each occurrence, H, halo, -CN, 3-6 membered heterocyclyl, C_{1-3}alkyl, or C_{1-3}alkoxy, wherein the C_{1-3}alkyl of R^5 is optionally substituted with one or more halo, or -OH and wherein the C_{1-3}alkoxy is optionally substituted with one or more halo.

30. The compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, is selected from Compounds 1-472 of Table 1.

31. A method for preparing a compound of formula (II), as recited in claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, comprises a step of reacting a compound of formula (II'-A):



(II'-A),

wherein:

m is an integer from 0 to 4;

n is an integer from 0 to 2;

p is an integer from 0 to 10;

R^1, if present is, independently at each occurrence selected from the group consisting of halo, -CN, C_{1-6}alkoxy, and C_{1-6}alkyl, wherein

the C_{1-6}alkoxy of R^1 is optionally substituted with one or more halo, and

the C_{1-6}alkyl of R^1 is optionally substituted with one or more halo;

R^2 is H, C_{1-6}alkyl, C_{3-10}cycloalkyl, or 3-15 membered heterocyclyl, wherein

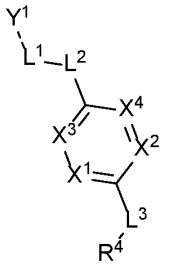
the C_{1-6}alkyl of R^2 is optionally substituted with one or more deuterium, halo, -OH, $-NH_2$, or C_{1-6}alkoxy, and

the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more -OH;

R^3, if present, is C_{1-6}alkyl;

with:

a compound of formula (II'-B):



(II'-B),

wherein:

the dashed line represents a single or double bond;

Y^1 is halo, oxo, or a sulfonate ester

L^1 is C_{1-6}alkylene, wherein

the C_{1-6}alkylene of L^1 is optionally substituted with one or more deuterium or C_{1-6}alkyl, and wherein

the C_{1-6}alkyl is further optionally substituted with one or more -OH or C_{1-6}alkoxy;

L^2 is O or $N(R^x)$, wherein R^x is H or C_{1-6}alkyl; and

either

(1) L^3 is absent or is O, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, or C_{1-6}alkylene, wherein

the C_{3-10}cycloalkyl of L^3 is optionally substituted with one or more –OH or C_{1-6}alkyl,

the C_{1-6}alkylene of L^3 is optionally substituted with one or more –OH or C_{1-6}alkyl, wherein

the C_{1-6}alkyl is optionally substituted with one or more -OH, and

the 3-10 membered heterocyclyl of L^3 is optionally substituted with one or more –OH or C_{1-6}alkyl;

X^1 and X^2 are each independently N or $C(R^5)$; and

R^4 is:

(i) -$S(O)_2$-R^a;

(ii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^4 is optionally substituted with one or more C_{1-6}alkyl;

(iii) -$N(R^d)_2$, wherein R^d is independently at each occurrence H, C_{1-6} alkyl, or -$S(O)_2$-R^a, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more -OH,

(iv) -NS(O)-(C_{1-6}alkyl)$_2$, wherein the C_{1-6}alkyl is optionally substituted with one or more –OH,

(v) -C(O)-$N(R^e)_2$ wherein R^e is independently at each occurrence H, C_{1-6} alkyl, or 3-10 membered heterocycle, wherein

the 3-10 membered heterocycle of R^e is optionally substituted with one or more oxo, or both R^e together with the N to which they are attached are taken together to form a 3-10 membered heterocyclyl, wherein

the 3-10 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, -NH-$S(O)_2$-R^a, or -$S(O)_2$-R^a,

(vi) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl, -OH , oxo or -$S(O)_2R^a$,

(vii) -S(O)-N(C_{1-6}alkyl)-(C_{1-6}alkyl),

(viii) -CN,

(ix) -$(CH_2)_q$OH, wherein *q* is an integer from 0-6,

(x) -C(O)-C_{1-6}alkyl, or

(xi) -P(O)(C_{1-6}alkyl)$_2$;

or

(2) L^3 is absent; and

one of X^1 and X^2 is N or C(R^5); and

the other of X^1 and X^2 is N or C that is taken together with R^4, and the atoms to which they are attached, to form a 5-10 membered heterocyclyl or a 5-20 membered heteroaryl, wherein

the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein

R^b is, independently at each occurrence, selected from the group consisting of -OH, halo, oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -$S(O)_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, OH, $-S(O)_2-C_{1-6}$alkyl, or C_{3-10}cycloalkyl, and wherein

the C_{3-10}cycloalkyl of the C_{1-6}alkyl of R^b is further optionally substituted with one or more C_{1-6}alkyl or -OH and

the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more -OH, C_{3-10}cycloalkyl, or C_{1-6}alkyl, and wherein

the C_{1-6}alkyl of the C_{3-10}cycloalkyl of R^b is further optionally substituted with one or more -OH, deuterium, or halo, and

the 5-20 membered heteroaryl is optionally substituted with one or more R^c, wherein

R^c is, independently at each occurrence, selected from the group consisting of halo, C_{1-6}alkyl, $-C(O)-C_{1-6}$alkyl, $-C(O)-NH_2$, $-C(O)-NH(C_{1-6}alkyl)$, $-C(O)-N(C_{1-6}alkyl)_2$, $-S(O)_2-R^a$, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more $-S(O)_2-C_{1-6}$alkyl,

the C_{3-10}cycloalkyl of R^c is optionally substituted with one or more -OH or C_{1-6}alkyl, and

the 3-10 membered heterocyclyl of R^c is optionally substituted with one or more -OH or C_{1-6}alkyl, and wherein

the C_{1-6}alkyl of the 3-10 membered heterocyclyl of R^c is further optionally substituted with one or more -OH;

R^a is, independently at each occurrence:

(i) C_{1-6}alkyl optionally substituted with one or more halo, -OH, $-S(O)_2-C_{1-6}$alkyl, or $-N(C_{1-6}alkyl)-C(O)-C_{1-6}$alkyl,

(ii) C_{3-10}cycloalkyl optionally substituted with one or more -OH, $-C(O)_2-C_{1-6}$alkyl, $-C(O)-NH(C_{1-6}alkyl)$, $-C(O)-N(C_{1-6}alkyl)_2$, or $-C(O)-C_{3-10}$heterocyclyl, or C_{1-6}alkyl, wherein

the C_{1-6}alkyl is optionally substituted with one or more -OH,

(iii) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl, or

(iv) $NH(C_{1-6}alkyl)$;

R^5 is, independently at each occurrence, H, halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein

the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo or -OH, and

the C_{1-6}alkoxy of R^5 is optionally substituted with one or more halo;

X^3 is N or $C(R^6)$;

X^4 is N or $C(R^7)$;

and

R^6 and R^7 are each independently H or halo;

to give a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

32. The method of claim 31, wherein the compound of claim 1 is prepared by a step comprising:

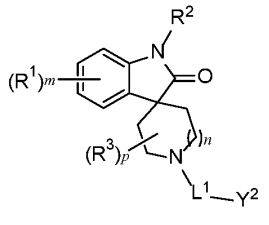
a) alkylation of an amine of formula (II'-A) with an alkyl halide, or sulfonate ester compound of formula (II'-B) in the presence of an inorganic base; or

b) reductive amination of a ketone of formula (II'-B) with an amine of formula (II'-A).

33. The method of claim 32, wherein the inorganic base is selected from the group consisting of potassium carbonate, and sodium bicarbonate.

34. The method of claim 32, wherein the reductive amination proceeds under the action of sodium triacetoxyborohydride, titanium tetraiopropoxide and acetic acid.

35. A method for preparing a compound of formula (II), as recited in claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, comprising a step of reacting a compound of formula (II'-C):



(II'-C),

wherein:

m is an integer from 0 to 4;

n is an integer from 0 to 2;

p is an integer from 0 to 10;

R^1, if present is, independently at each occurrence selected from the group consisting of halo, -CN, $C_{1\text{-}6}$alkoxy, and $C_{1\text{-}6}$alkyl, wherein

the $C_{1\text{-}6}$alkoxy of R^1 is optionally substituted with one or more halo, and

the $C_{1\text{-}6}$alkyl of R^1 is optionally substituted with one or more halo;

R^2 is H, $C_{1\text{-}6}$alkyl, $C_{3\text{-}10}$cycloalkyl, or 3-15 membered heterocyclyl, wherein

the $C_{1\text{-}6}$alkyl of R^2 is optionally substituted with one or more deuterium, halo, -OH, $-NH_2$, or $C_{1\text{-}6}$alkoxy, and

the $C_{3\text{-}10}$cycloalkyl of R^2 is optionally substituted with one or more -OH;

R^3, if present, is $C_{1\text{-}6}$alkyl;

L^1 is $C_{1\text{-}6}$alkylene, wherein

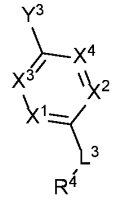
the $C_{1\text{-}6}$alkylene of L^1 is optionally substituted with one or more deuterium or $C_{1\text{-}6}$alkyl, and wherein

the $C_{1\text{-}6}$alkyl is further optionally substituted with one or more -OH or $C_{1\text{-}6}$alkoxy; and

Y^2 is halo, -OH or $-NH_2$;

with:

a compound of formula (II'-D):



(II'-D),

wherein:

Y^3 is -OH or $-NH(R^x)$, wherein each R^x is independtly H or $C_{1\text{-}6}$alkyl; and

either

(1) L^3 is absent or is O, $C_{3\text{-}10}$cycloalkyl, 3-10 membered heterocyclyl, or $C_{1\text{-}6}$alkylene, wherein

the $C_{3\text{-}10}$cycloalkyl of L^3 is optionally substituted with one or more –OH or $C_{1\text{-}6}$alkyl,

the $C_{1\text{-}6}$alkylene of L^3 is optionally substituted with one or more –OH or $C_{1\text{-}6}$alkyl, wherein

the $C_{1\text{-}6}$alkyl is optionally substituted with one or more -OH, and

the 3-10 membered heterocyclyl of L^3 is optionally substituted with one or more –OH or C_{1-6}alkyl;

X^1 and X^2 are each independently N or $C(R^5)$; and

R^4 is:

(i) $-S(O)_2-R^a$;

(ii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^4 is optionally substituted with one or more C_{1-6}alkyl;

(iii) $-N(R^d)_2$, wherein R^d is independently at each occurrence H, C_{1-6} alkyl, or $-S(O)_2-R^a$, wherein the C_{1-6}alkyl of R^d is optionally substituted with one or more -OH,

(iv) $-NS(O)-(C_{1-6}alkyl)_2$, wherein the C_{1-6}alkyl is optionally substituted with one or more –OH,

(v) $-C(O)-N(R^e)_2$ wherein R^e is independently at each occurrence H, C_{1-6} alkyl, or 3-10 membered heterocycle, wherein

the 3-10 membered heterocycle of R^e is optionally substituted with one or more oxo, or both R^e together with the N to which they are attached are taken together to form a 3-10 membered heterocyclyl, wherein

the 3-10 membered heterocyclyl is optionally substituted with one or more halo, oxo, -OH, NH_2, $-NH-S(O)_2-R^a$, or $-S(O)_2-R^a$,

(vi) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl, -OH, oxo or $-S(O)_2R^a$,

(vii) $-S(O)-N(C_{1-6}alkyl)-(C_{1-6}alkyl)$,

(viii) -CN,

(ix) $-(CH_2)_qOH$, wherein q is an integer from 0-6,

(x) $-C(O)-C_{1-6}$alkyl, or

(xi) $-P(O)(C_{1-6}alkyl)_2$;

or

(2) L^3 is absent; and

one of X^1 and X^2 is N or $C(R^5)$; and

the other of X^1 and X^2 is N or C that is taken together with R^4, and the atoms to which they are attached, to form a 5-10 membered heterocyclyl or a 5-20 membered heteroaryl, wherein

the 5-10 membered heterocyclyl is optionally substituted with one or more R^b, wherein

R^b is, independently at each occurrence, selected from the group consisting of -OH, halo, oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -S(O)$_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, OH, -S(O)$_2$-C_{1-6}alkyl, or C_{3-10}cycloalkyl, and wherein

the C_{3-10}cycloalkyl of the C_{1-6}alkyl of R^b is further optionally substituted with one or more C_{1-6}alkyl or -OH and

the C_{3-10}cycloalkyl of R^b is optionally substituted with one or more -OH, C_{3-10}cycloalkyl, or C_{1-6}alkyl, and wherein

the C_{1-6}alkyl of the C_{3-10}cycloalkyl of R^b is further optionally substituted with one or more -OH, deuterium, or halo, and

the 5-20 membered heteroaryl is optionally substituted with one or more R^c, wherein

R^c is, independently at each occurrence, selected from the group consisting of halo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -S(O)$_2$-R^a, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more -S(O)$_2$-C_{1-6}alkyl,

the C_{3-10}cycloalkyl of R^c is optionally substituted with one or more -OH or C_{1-6}alkyl, and

the 3-10 membered heterocyclyl of R^c is optionally substituted with one or more -OH or C_{1-6}alkyl, and wherein

the C_{1-6}alkyl of the 3-10 membered heterocyclyl of R^c is further optionally substituted with one or more -OH;

R^a is, independently at each occurrence:

(i) C_{1-6}alkyl optionally substituted with one or more halo, -OH, -S(O)$_2$-C_{1-6}alkyl, or -N(C_{1-6}alkyl)-C(O)-C_{1-6}alkyl,

(ii) C_{3-10}cycloalkyl optionally substituted with one or more -OH, -C(O)$_2$-C_{1-6}alkyl, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, or –C(O)-C_{3-10}heterocyclyl, or C_{1-6}alkyl, wherein

the C_{1-6}alkyl is optionally substituted with one or more -OH,

(iii) 3-10 membered heterocyclyl optionally substituted with one or more C_{1-6}alkyl, or

(iv) NH(C_{1-6}alkyl);

R^5 is, independently at each occurrence, H, halo, -CN, 3-10 membered heterocyclyl, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein

the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo or -OH, and

the C_{1-6}alkoxy of R^5 is optionally substituted with one or more halo;

X^3 is N or C(R^6);

X^4 is N or C(R^7);

and

R^6 and R^7 are each independently H or halo;

to give a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

36. The method of claim 35, wherein the compound of claim 1 is prepared by a step comprising:

a) coupling of an alcohol compound of formula (II'-C) with a phenol compound of formula (II'-D), or a heterocyclic variant, under Mitsunobu-type reaction conditions; or

b) reacting an alkyl halide compound of formula (II'-C) with a phenol or amine compound of formula (II'-D), in the presence of a catalyst.

37. The method of claim 36, wherein the Mitsunobi-type reaction conditions comprises coupling of an alcohol compound of formula (II'-C) with a phenol compound of formula (II'-D), or a heterocyclic variant, in the presence of triphenylphosphine and diisopropyl azodicarboxylate.

38. The method of claim 37, wherein the catalyst is silver oxide or potassium carbonate.

39. A pharmaceutical composition, comprising (i) a compound of any one of claims 1-30, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) one or more pharmaceutically acceptable excipients.

40. A method of modulating APOL1 in a cell, comprising exposing the cell to a composition comprising an effective amount of a compound of any one or claims 1-30, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical

composition of claim 39.

41. A method of inhibiting APOL1 in a cell, comprising exposing the cell to a composition comprising an effective amount of a compound of any one or claims 1-30 or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition of claim 39.

42. A method of treating an APOL1-mediated disease, disorder, or condition in an individual in need thereof, comprising administering to the individual a compound of any one of claims 1-30, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition of claim 39.

43. The method of claim 42, 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.

44. The method of claim 42 or claim 43, wherein the disease, disorder, or condition is a kidney disease.

45. The method of any one of claims 40-44, wherein the disease, disorder, or condition is a chronic kidney disease (CKD).

46. A method of delaying the development of an APOL1-mediated disease, disorder, or condition, comprising administering a compound of any one of claims 1-30, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition of claim 39, to an individual who is at risk of developing an APOL1-mediated disease, disorder, or condition.

47. The method of claim 46, wherein the APOL1-mediated disease, disorder, or condition is a kidney disease.

48. The method of claim 46 or claim 47, wherein the APOL1-mediated disease, disorder, or condition is a chronic kidney disease.

49. The method of claim 46, wherein the APOL1-mediated 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.

50. The method of any one of claims 40-49, wherein the individual has an APOL1 mutation.

51. The method of claim 50, wherein the APOL1 mutation is a gain-of-function mutation.

52. The method of any one of claims 42-51, wherein a therapeutically effective amount of a compound of any one of claims 1-30, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition of claim 39, is administered.

53. A kit, comprising (i) a compound of any one of claims 1-30, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition of claim 39, and (ii) instructions for use in treating an APOL1-mediated disease, disorder, or condition in an individual in need thereof.

54. The kit of claim 53, wherein the disease, disorder, or condition is a kidney disease.

55. The kit of claim 53 or claim 54, wherein the disease, disorder, or condition is a chronic kidney disease (CKD).

56. The kit of any one of claims 53-55, 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.

57. The kit of any one of claims 53-56, wherein the individual has an APOL1 mutation.

58. The kit of claim 57, wherein the APOL1 mutation is a gain-of-function mutation.