

SARM1 MODULATORS, PREPARATIONS, AND USES THEREOF**Related Applications**

[0001] This application claims priority to International Application No. PCT/CN2022/097337, filed on June 7, 2022, and International Application No. 5 PCT/CN2023/083360, filed on March 23, 2023. The contents of both applications are incorporated by reference in their entireties.

Field of the Disclosure

[0002] The present disclosure relates to compounds that modulate SARM1, compositions comprising the compounds, methods of preparing the compounds, and 10 methods of using the compounds to treat various diseases or conditions, e.g., those caused by axonal degeneration.

Background of the Disclosure

[0003] Axonal degeneration causes disease progression and accumulation of disability in many degenerative diseases of the peripheral nervous system (PNS) and central nervous 15 systems (CNS), such as multiple sclerosis, Parkinson's disease, and amyotrophic lateral sclerosis (ALS), or acute conditions such as traumatic brain injury. (Hughes 2021 (R. Hughes et al., Small Molecule SARM1 Inhibitors Recapitulate the SARM1-/- Phenotype and Allow Recovery of a Metastable Pool of Axons Fated to Degenerate, Cell Rep. 2021 Jan 5;34(1):108588.); Bosanac 2021 (T. Bosanac et al., Pharmacological SARM1 inhibition protects axon structure and function 20 in paclitaxel-induced peripheral neuropathy, Brain, Vol. 144, Issue 10, 2021, pages 3226-3238)). Therefore, axonal protection is an important neuroprotective approach to treatment of chronic and acute CNS and PNS neurodegenerative disorders. (Hughes 2021; Bosanac 2021).

[0004] SARM1 (Sterile Alpha and TIR Motif-containing 1) is a unique member of the Myd88 family of adaptor proteins and is considered a major driver of an evolutionarily conserved 25 program of axonal degeneration downstream of chemical, inflammatory, mechanical, or metabolic insults to the axon. (Hughes 2021; Bosanac 2021). SARM1 has been recognized as a central mediator of axonal degeneration in a number of diseases or conditions, including ALS, Parkinson's disease, multiple sclerosis, traumatic brain injury, and diabetic neuropathy, as well as chemotherapy induced peripheral neuropathy (CIPN), which is a major cause of morbidity 30 and the main cause of dose reductions and discontinuations in cancer treatment. (Hughes 2021; Bosanac 2021). SARM1 is a compelling target to treat neurodegeneration characterized by axonopathies of the peripheral and central nervous systems

[0005] SARM1 contains a mitochondrial targeting sequence, an N-terminal domain with armadillo repeats (ARM), two sterile α -motif (SAM) domains, and a Toll/interleukin-1 receptor (TIR) domain (Gerdt 2013 (J. Gerdt et al., Sarm1-mediated axon degeneration requires both SAM and TIR interactions. *J Neurosci.* 2013 Aug 14;33(33):13569-80.)) The SARM1 TIR domain is a NAD⁺ hydrolase (NADase), which converts the NAD⁺ to ADPR or cADPR and NAM (Sporny 2019 (M. Sporny et al., Structural Evidence for an Octameric Ring Arrangement of SARM1. *J Mol Biol.* 2019 Sep 6;431(19):3591-3605.)). This NADase activity is essential for its axonal degenerative function. (Bosanac 2021). The activity of SARM1 also depends on the oligomerization formed through the SAM domains (Sporny 2019) and is autoinhibited by the ARM domain (Chen (2021) (C. Shen et al., Multiple domain interfaces mediate SARM1 autoinhibition. *Proc Natl Acad Sci U S A.* 2021 Jan 26;118(4).)).

[0006] Certain SARM1 inhibitors are disclosed by Bosanac 2021, Hughes 2021, Sporny 2020 (M. Sporny et al, Structural basis for SARM1 inhibition and activation under energetic stress. *Elife.* 2020 Nov 13;9:e62021. doi: 10.7554/eLife.62021. PMID: 33185189; PMCID: PMC7688312.), WO 2018/057989 A1, WO 2020/081923 A1, WO 2021/142006 A1, WO2021207302A1, and WO2021207308A1. Certain dipeptidyl peptidase inhibitors (e.g., biphenyl or phenyl benzo imidazole derivatives) are disclosed in US 2005/0272765 A1. Certain benzyl benzoxazol derivatives as Met-kinase inhibitors are disclosed in WO 2008/148449 A1. Certain dihydroisoquinolinone derivatives and combinatorial libraries thereof are described in WO 01/14879. Certain compositions for promoting readthrough of premature termination codons, and methods of using the same are described in WO 2017/049409. Certain nitrogen-containing heterocyclic compounds having nematocidal properties, preparations and uses thereof are described in CN 108276352.

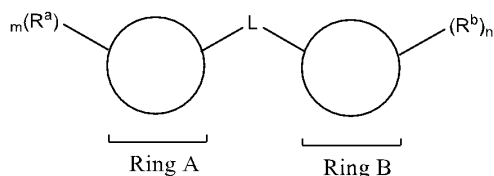
[0007] The present disclosure describes SARM1 inhibitors that can be used to prevent axonal degeneration in peripheral and central axonopathies and to provide a transformational disease-modifying treatment for the related diseases or conditions.

Summary of the Disclosure

[0008] One aspect of this disclosure provides a compound selected from compounds of Formulae 1, 2, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2L, 2m, 3, 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3L, 4, 5, 6, 7, 7a, 7b, 8, 8a, 9, 9a, 10, 11, 12, 13, 13a, 13b, 14, 14a, 14b, 14c, 14d, 14e, 14f, 14g, 14h-1, 14h-2, 14i, 14j, 15, 15a, 16-1, 16-2, 16-1a, 16-2a, 17, 17a, 18, 18a, 19, 20, 21, 21a, 21b, 22, 22a, 23, 23a, 24, 25, 26, 27, 28-1, 28-2, 29-1, 29-2, 29-3, 30-1, 30-

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10 Formula 1:



Formula 1

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

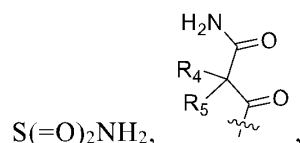
15 Ring A is phenyl, a 5- to 10-membered heteroaryl ring, a 5 to 10-membered carbocyclic ring or a 5 to 10-membered heterocyclic ring;

Ring B is phenyl, a 9- to 11-membered aryl ring, a 9- to 11-membered heteroaryl ring, or a 9- to 11-membered heterocyclic ring;

20 R^a is selected from =O, C_3 - C_6 cycloalkyl, $-O(C_1$ - C_4 alkyl), $COOH$, CN , $CONH_2$, $-C(=O)NH(C_1$ - C_4 alkyl), $-C(=O)N(C_1$ - C_4 alkyl) $_2$, $-C(=O)O(C_1$ - C_4 alkyl), halogen, and C_1 - C_4 alkyl optionally substituted with 1 to 3 groups selected from halogen, $-OH$, cyclopropyl, oxetanyl, and azetidiny;

25 R^b is selected from =O, OH , halogen, CN , $-C(=O)NH_2$, $-C(=O)NH(C_1$ - C_4 alkyl), $-C(=O)O(C_1$ - C_4 alkyl), optionally substituted C_3 - C_6 cycloalkyl, optionally substituted C_3 - C_6 heterocyclyl, optionally substituted C_5 - C_6 heteroaryl, $-O(C_1$ - C_4 alkyl), $-C(=O)(C_1$ - C_4 alkyl), $-C(=O)($ optionally substituted C_3 - C_6 cycloalkyl), $-C(=O)($ optionally substituted 5- to 6-membered heterocyclyl), $-C(=O)($ optionally

substituted 5- to 6-membered heteroaryl), $-\text{C}(=\text{O})(\text{CH}_2)_p\text{C}(=\text{O})\text{NH}_2$, $-\text{NHC}(=\text{O})(\text{C}_1\text{-C}_4 \text{ alkyl})$, $-\text{C}(=\text{O})\text{N}(\text{C}_1\text{-C}_4 \text{ alkyl})_2$, $-\text{C}(=\text{O})\text{NH}(\text{CH}_2)_p\text{OH}$, $-\text{S}(=\text{O})_2\text{NH}_2$,



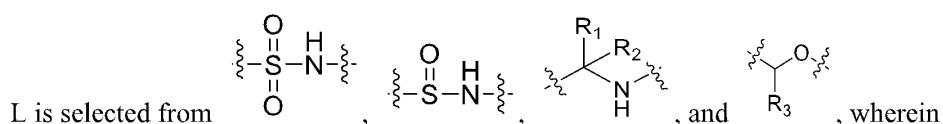
$\text{C}_1\text{-C}_4$ alkyl optionally substituted with 1 to 3 groups selected from halogen, NH_2 , OH , OCH_3 , $-\text{C}(=\text{O})\text{NH}(\text{C}_1\text{-C}_4 \text{ alkyl})$, $-\text{C}(=\text{O})\text{O}(\text{C}_1\text{-C}_4 \text{ alkyl})$, $-\text{C}(=\text{O})\text{N}(\text{C}_1\text{-C}_4 \text{ alkyl})_2$, $-\text{COOH}$, $-\text{C}(=\text{O})\text{NH}_2$, CN , $\text{C}_3\text{-C}_5$ cycloalkyl, phenyl, $-\text{C}(=\text{O})(\text{C}_1\text{-C}_4 \text{ alkyl})$, $-\text{C}(=\text{O})(\text{C}_3\text{-C}_6 \text{ cycloalkyl})$, $-\text{C}(=\text{O})(5\text{- to } 6\text{-membered heterocyclyl})$, $-\text{C}(=\text{O})(\text{optionally substituted } 5\text{- to } 6\text{-membered heteroaryl})$, $\text{C}(=\text{O})\text{NH}(\text{CH}_2)_p\text{OH}$, and 5- to 6-membered heteroaryl,

5- to 6- membered heteroaryl optionally substituted with 1 to 2 groups selected from $\text{C}_1\text{-C}_3$ alkyl, $=\text{O}$, $-\text{NH}_2$, $-\text{CN}$, $-\text{CONH}_2$, halogen, and

4- to 6-membered heterocyclyl optionally substituted with 1 to 2 groups selected from $=\text{O}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{CN}$, $-\text{CONH}_2$, halogen, and $\text{C}_1\text{-C}_3$ alkyl, or

two R^b attached to the same position on Ring B join to form a $\text{C}_3\text{-C}_6$ cycloalkyl,

wherein R_4 and R_5 are each independently selected from H and C_1 to C_3 alkyl or R_4 and R_5 join to form a 3- to 5-membered cycloalkyl;



R_1 is H, D, or $\text{C}_1\text{-C}_6$ alkyl, and R_2 is selected from CN , $\text{C}_1\text{-C}_6$ alkenyl, $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_3\text{-C}_6$ heterocyclyl, 5- or 6-membered heteroaryl,

phenyl optionally substituted with 1 to 3 groups selected from $\text{C}_1\text{-C}_4$ alkyl and halogen, and

$\text{C}_1\text{-C}_6$ alkyl optionally substituted with 1 to 3 groups selected from halogen, OH , CN , $-\text{SO}_2\text{CH}_3$, $-\text{NHSO}_2\text{CH}_3$, $-\text{CONH}_2$, OCH_3 , and phenyl, or

R_1 and R_2 join to form a 3- to 6-membered carbocyclyl or 3- to 6-membered

heterocyclyl;

R_3 is $\text{C}_1\text{-C}_4$ alkyl optionally substituted with 1 to 3 groups selected from halogen,

O(C₁-C₃ alkyl), OH and NH₂;

m is an integer selected from 0, 1, 2, 3, and 4;

n is an integer selected from 0, 1, 2, 3, and 4, and

p is an integer selected from 1, 2, 3, and 4.

5 provided that the compound is not any of Compound 1A to Compound 121A.

[0009] In one aspect of the disclosure, the compounds of the Formulae disclosed herein are selected from Compounds 1 to 391 shown in Table 1, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

10 [0010] In some embodiments, the disclosure provides pharmaceutical compositions comprising a compound of Formulae 1, 2, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2L, 2m, 3, 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3L, 4, 5, 6, 7, 7a, 7b, 8, 8a, 9, 9a, 10, 11, 12, 13, 13a, 13b, 14, 14a, 14b, 14c, 14d, 14e, 14f, 14g, 14h-1, 14h-2, 14i, 14j, 15, 15a, 16-1, 16-2, 16-1a, 16-2a, 17, 17a, 18, 18a, 19, 20, 21, 21a, 21b, 22, 22a, 23, 23a, 24, 25, 26, 27, 28-1, 28-2, 29-1, 29-2, 29-3, 30-1, 30-2, 30-3, 30-4, 30-5, 31-1, 31-2, 32-1, 32-2, 32-3, 32-4, 32-5, 33-1, 33-2, 33-3, 34-1, 34-2, 34-3, 34-4, 34-5, 34-6, 35-1, 35-2, 35-3, 35-4, 36-1, 36-2, 36-3, 37-1, 37-2, 37-3, 37-4, 37-5, 37-6, 38-1, 38-2, 38-3, 39-1, 39-2, 39-3, 39-4, 40-1, 40-2, 40-3, 41-1, 41-2, 41-3, 41-4, 41-5, 42-1, 42-2, 42-3, 43-1, 43-2, 43-3, 43-4, 44-1, 44-2, 44-3, 44-4, 44-5, 44-6, 44-7, 44-8, 44-9, 44-10, 44-11, 44-12, 44-13, 44-14, 45-1, 45-2, 46-1, 46-2, and 46-3 (e.g.,
15 2, 29-1, 29-2, 29-3, 30-1, 30-2, 30-3, 30-4, 30-5, 31-1, 31-2, 32-1, 32-2, 32-3, 32-4, 32-5, 33-1, 33-2, 33-3, 34-1, 34-2, 34-3, 34-4, 34-5, 34-6, 35-1, 35-2, 35-3, 35-4, 36-1, 36-2, 36-3, 37-1, 37-2, 37-3, 37-4, 37-5, 37-6, 38-1, 38-2, 38-3, 39-1, 39-2, 39-3, 39-4, 40-1, 40-2, 40-3, 41-1, 41-2, 41-3, 41-4, 41-5, 42-1, 42-2, 42-3, 43-1, 43-2, 43-3, 43-4, 44-1, 44-2, 44-3, 44-4, 44-5, 44-6, 44-7, 44-8, 44-9, 44-10, 44-11, 44-12, 44-13, 44-14, 45-1, 45-2, 46-1, 46-2, and 46-3 (e.g.,
20 Compounds 1 to 391) and Compounds 1A to 121A disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical compositions may comprise a compound selected from Compounds 1 to 391 and Compounds 1A to 121A shown below, a tautomer thereof, a
25 solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, and a pharmaceutically acceptable carrier. These compositions may further comprise an additional active pharmaceutical agent.

[0011] Another aspect of the disclosure provides methods of treating a disease or condition, comprising administering to a subject in need thereof, a therapeutically effective
30 amount of a compound of Formulae 1, 2, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2L, 2m, 3, 3a,

3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3L, 4, 5, 6, 7, 7a, 7b, 8, 8a, 9, 9a, 10, 11, 12, 13, 13a, 13b, 14, 14a, 14b, 14c, 14d, 14e, 14f, 14g, 14h-1, 14h-2, 14i, 14j, 15, 15a, 16-1, 16-2, 16-1a, 16-2a, 17, 17a, 18, 18a, 19, 20, 21, 21a, 21b, 22, 22a, 23, 23a, 24, 25, 26, 27, 28-1, 28-2, 29-1, 29-2, 29-3, 30-1, 30-2, 30-3, 30-4, 30-5, 31-1, 31-2, 32-1, 32-2, 32-3, 32-4, 32-5, 33-1, 33-2, 33-3, 34-
5 1, 34-2, 34-3, 34-4, 34-5, 34-6, 35-1, 35-2, 35-3, 35-4, 36-1, 36-2, 36-3, 37-1, 37-2, 37-3, 37-4, 37-5, 37-6, 38-1, 38-2, 38-3, 39-1, 39-2, 39-3, 39-4, 40-1, 40-2, 40-3, 41-1, 41-2, 41-3, 41-4, 41-5, 42-1, 42-2, 42-3, 43-1, 43-2, 43-3, 43-4, 44-1, 44-2, 44-3, 44-4, 44-5, 44-6, 44-7, 44-8, 44-9, 44-10, 44-11, 44-12, 44-13, 44-14, 45-1, 45-2, 46-1, 46-2, and 46-3 (e.g., Compounds 1 to 391) and Compounds 1A to 121A disclosed herein, a tautomer thereof, a solvate or
10 stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the compound, tautomer, solvate, stereoisomer, and pharmaceutically acceptable salt, wherein the disease or condition is selected amyotrophic lateral sclerosis (ALS), Parkinson's disease, Parkinsonian syndromes, ischemia, stroke, herpes infection, a demyelinating disease such
15 as multiple sclerosis, traumatic brain injury, sepsis, a chronic disease of PNS including inherited neuropathies, such as, but is not limited to Charcot-Marie-Tooth disease and chronic inflammatory demyelinating polyneuropathy (CIDP), an optic nerve disorder such as glaucoma, and retinal ganglion degeneration, colitis a metabolic disease or disorder such as diabetic neuropathy, nonalcoholic fatty liver disease (NAFLD) and nonalcoholic
20 steatohepatitis (NASH) and a peripheral neuropathy like CIPN induced by various drugs.

[0012] A further aspect of the disclosure provides methods of treating a disease or condition caused by axonal degeneration, or neuronal damage mediated by SARM1 comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of Formulae 1, 2, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2L, 2m, 3, 3a, 3b, 3c,
25 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3L, 4, 5, 6, 7, 7a, 7b, 8, 8a, 9, 9a, 10, 11, 12, 13, 13a, 13b, 14, 14a, 14b, 14c, 14d, 14e, 14f, 14g, 14h-1, 14h-2, 14i, 14j, 15, 15a, 16-1, 16-2, 16-1a, 16-2a, 17, 17a, 18, 18a, 19, 20, 21, 21a, 21b, 22, 22a, 23, 23a, 24, 25, 26, 27, 28-1, 28-2, 29-1, 29-2, 29-3, 30-1, 30-2, 30-3, 30-4, 30-5, 31-1, 31-2, 32-1, 32-2, 32-3, 32-4, 32-5, 33-1, 33-2, 33-3, 34-1, 34-2, 34-3, 34-4, 34-5, 34-6, 35-1, 35-2, 35-3, 35-4, 36-1, 36-2, 36-3, 37-1, 37-2, 37-3, 37-4, 37-5, 37-6,
30 38-1, 38-2, 38-3, 39-1, 39-2, 39-3, 39-4, 40-1, 40-2, 40-3, 41-1, 41-2, 41-3, 41-4, 41-5, 42-1, 42-2, 42-3, 43-1, 43-2, 43-3, 43-4, 44-1, 44-2, 44-3, 44-4, 44-5, 44-6, 44-7, 44-8, 44-9, 44-10, 44-11, 44-12, 44-13, 44-14, 45-1, 45-2, 46-1, 46-2, and 46-3 (e.g., Compounds 1 to 391)

and Compounds 1A to 121A disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the compound, tautomer, solvate, stereoisomer, and pharmaceutically acceptable salt.

5 [0013] In some embodiments, the methods of treatment comprise administering to a subject in need thereof, a compound selected from Compounds 1 to 391 and Compounds 1A to 121A shown below, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the compound, tautomer, solvate,
10 stereoisomer, and pharmaceutically acceptable salt.

 [0014] In some embodiments, the methods of treatment comprise administration of an additional active pharmaceutical agent to the subject in need thereof, either in the same pharmaceutical composition as a compound of Formulae 1, 2, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2L, 2m, 3, 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3L, 4, 5, 6, 7, 7a, 7b, 8, 8a, 9,
15 9a, 10, 11, 12, 13, 13a, 13b, 14, 14a, 14b, 14c, 14d, 14e, 14f, 14g, 14h-1, 14h-2, 14i, 14j, 15, 15a, 16-1, 16-2, 16-1a, 16-2a, 17, 17a, 18, 18a, 19, 20, 21, 21a, 21b, 22, 22a, 23, 23a, 24, 25, 26, 27, 28-1, 28-2, 29-1, 29-2, 29-3, 30-1, 30-2, 30-3, 30-4, 30-5, 31-1, 31-2, 32-1, 32-2, 32-3, 32-4, 32-5, 33-1, 33-2, 33-3, 34-1, 34-2, 34-3, 34-4, 34-5, 34-6, 35-1, 35-2, 35-3, 35-4, 36-1, 36-2, 36-3, 37-1, 37-2, 37-3, 37-4, 37-5, 37-6, 38-1, 38-2, 38-3, 39-1, 39-2, 39-3, 39-4, 40-1, 40-2, 40-3, 41-
20 1, 41-2, 41-3, 41-4, 41-5, 42-1, 42-2, 42-3, 43-1, 43-2, 43-3, 43-4, 44-1, 44-2, 44-3, 44-4, 44-5, 44-6, 44-7, 44-8, 44-9, 44-10, 44-11, 44-12, 44-13, 44-14, 45-1, 45-2, 46-1, 46-2, and 46-3 (e.g., Compounds 1 to 391) and Compounds 1A to 121A disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or in a separate composition. In some
25 embodiments, the methods of treatment comprise administering a compound selected from Compounds 1 to 391 and Compounds 1A to 121A shown below, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing with an additional active pharmaceutical agent either in the same pharmaceutical composition or in a separate composition. When administered as a separate
30 composition, the additional therapeutic agent may be administered prior to, at the same time as, or following administration of the compound, tautomer, solvate, stereoisomer, or a pharmaceutically acceptable salt disclosed herein.

[0015] Also disclosed herein are methods of modulating, e.g., inhibiting, SARM1 in a subject in need thereof, comprising contacting the subject with a compound of Formulae 1, 2, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2L, 2m, 3, 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3L, 4, 5, 6, 7, 7a, 7b, 8, 8a, 9, 9a, 10, 11, 12, 13, 13a, 13b, 14, 14a, 14b, 14c, 14d, 14e, 14f, 14g, 14h-1, 14h-2, 14i, 14j, 15, 15a, 16-1, 16-2, 16-1a, 16-2a, 17, 17a, 18, 18a, 19, 20, 21, 21a, 21b, 22, 22a, 23, 23a, 24, 25, 26, 27, 28-1, 28-2, 29-1, 29-2, 29-3, 30-1, 30-2, 30-3, 30-4, 30-5, 31-1, 31-2, 32-1, 32-2, 32-3, 32-4, 32-5, 33-1, 33-2, 33-3, 34-1, 34-2, 34-3, 34-4, 34-5, 34-6, 35-1, 35-2, 35-3, 35-4, 36-1, 36-2, 36-3, 37-1, 37-2, 37-3, 37-4, 37-5, 37-6, 38-1, 38-2, 38-3, 39-1, 39-2, 39-3, 39-4, 40-1, 40-2, 40-3, 41-1, 41-2, 41-3, 41-4, 41-5, 42-1, 42-2, 42-3, 43-1, 43-2, 43-3, 43-4, 44-1, 44-2, 44-3, 44-4, 44-5, 44-6, 44-7, 44-8, 44-9, 44-10, 44-11, 44-12, 44-13, 44-14, 45-1, 45-2, 46-1, 46-2, and 46-3 (e.g., Compounds 1 to 391) and Compounds 1A to 121A disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the compound, tautomer, solvate, stereoisomer, and pharmaceutically acceptable salt. In some embodiments, the methods of modulating, e.g., inhibiting, SARM1 in a subject in need thereof comprise contacting the subject with a compound selected from Compounds 1 to 391 and Compounds 1A to 121A shown below, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the compound, tautomer, solvate, stereoisomer, and pharmaceutically acceptable salt.

[0016] Also disclosed herein are methods of inhibiting or preventing axonal degeneration in a subject in need thereof, comprising contacting the subject with a compound of Formulae 1, 2, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2L, 2m, 3, 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3L, 4, 5, 6, 7, 7a, 7b, 8, 8a, 9, 9a, 10, 11, 12, 13, 13a, 13b, 14, 14a, 14b, 14c, 14d, 14e, 14f, 14g, 14h-1, 14h-2, 14i, 14j, 15, 15a, 16-1, 16-2, 16-1a, 16-2a, 17, 17a, 18, 18a, 19, 20, 21, 21a, 21b, 22, 22a, 23, 23a, 24, 25, 26, 27, 28-1, 28-2, 29-1, 29-2, 29-3, 30-1, 30-2, 30-3, 30-4, 30-5, 31-1, 31-2, 32-1, 32-2, 32-3, 32-4, 32-5, 33-1, 33-2, 33-3, 34-1, 34-2, 34-3, 34-4, 34-5, 34-6, 35-1, 35-2, 35-3, 35-4, 36-1, 36-2, 36-3, 37-1, 37-2, 37-3, 37-4, 37-5, 37-6, 38-1, 38-2, 38-3, 39-1, 39-2, 39-3, 39-4, 40-1, 40-2, 40-3, 41-1, 41-2, 41-3, 41-4, 41-5, 42-1, 42-2, 42-3, 43-1, 43-2, 43-3, 43-4, 44-1, 44-2, 44-3, 44-4, 44-5, 44-6, 44-7, 44-8, 44-9, 44-10, 44-11, 44-12, 44-13, 44-14, 45-1, 45-2, 46-1, 46-2, and 46-3 (e.g., Compounds 1 to 391) and

Compounds 1A to 121A disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the compound, tautomer, solvate, stereoisomer, and pharmaceutically acceptable salt. In some embodiments, the methods of
5 inhibiting or preventing axonal degeneration or neuronal damage mediated by SARM1 in a subject in need thereof comprise contacting the subject with a compound selected from Compounds 1 to 391 and Compounds 1A to 121A shown below, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the compound,
10 tautomer, solvate, stereoisomer, and pharmaceutically acceptable salt.

Detailed Description of the Disclosure

I. Definitions

[0017] The term "a" or "an" when referring to a noun as used herein encompasses the expression "at least one" and therefore encompasses both singular and plural units of
15 the noun. For example, "an additional pharmaceutical agent" means a single or two or more additional pharmaceutical agents.

[0018] The term "alkyl" refers to a hydrocarbon group selected from linear and branched saturated hydrocarbon groups, containing 1-20, e.g., 1-18, 1-12, 1-10, 1-8, 1-6, 1-4, or 1-3, carbon atoms. Examples of the alkyl group include methyl, ethyl, 1-propyl or n-propyl ("n-Pr"), 2-propyl or isopropyl ("i-Pr"), 1-butyl or n-butyl ("n-Bu"), 2-methyl-1-propyl or isobutyl ("i-Bu"), 1-methylpropyl or s-butyl ("s-Bu"), and 1,1-dimethylethyl or t-butyl ("t-Bu"). Other examples of an alkyl group include 1-pentyl, 2-pentyl, 3-pentyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 3-methyl-1-butyl, 2-methyl-1-butyl, 1-hexyl, 2-hexyl, 3-hexyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 3-methyl-3-pentyl, 2-methyl-3-pentyl, 2,3-dimethyl-2-
25 butyl, and 3,3-dimethyl-2-butyl groups. Lower alkyl contains 1-8, preferably 1-6, more preferably 1-4 carbon atoms, and more preferably 1-3 carbon atoms.

[0019] The term "alkenyl" refers to a hydrocarbon group selected from linear and branched hydrocarbon groups, comprising at least one C=C double bond and 2-20, e.g., 2-18, 2-12, 2-10, 2-8, 2-6, or 2-4, carbon atoms. Examples of the alkenyl group include ethenyl or vinyl,
30 prop-1-enyl, prop-2-enyl, 2-methylprop-1-enyl, but-1-enyl, but-2-enyl, but-3-enyl, buta-1,3-dienyl, 2-methylbuta-1,3-diene, hex-1-enyl, hex-2-enyl, hex-3-enyl, hex-4-enyl, and hexa-1,3-dienyl groups. Lower alkenyl contains 2-8, preferably 2-6, and more preferably 2-4 carbon atoms.

[0020] The term "alkynyl" refers to a hydrocarbon group selected from linear and branched hydrocarbon groups, comprising at least one C≡C triple bond and 2-20, e.g., 2-18, 2-12, 2-10, 2-8, 2-6, or 2-4, carbon atoms. Examples of the alkynyl group include ethynyl, 1-propynyl, 2-propynyl (propargyl), 1-butyne, 2-butyne, and 3-butyne groups. Lower alkynyl
5 contains 2-8, preferably 2-6, and more preferably 2-4 carbon atoms.

[0021] The term "heteroalkyl" refers to an alkyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by a heteroatom, e.g., nitrogen, oxygen, or sulfur, e.g., CH₃CH₂OH, CH₃CH₂OC₂H₅, CH₃CH₂SH, CH₃CH₂SC₂H₅, CH₃CH₂NH₂, CH₃CH₂NHC₂H₅, etc. In some embodiments, in addition to
10 the replacement of one or more of the constituent carbon atoms by nitrogen, oxygen, or sulfur, a heteroalkyl group is further optionally substituted as defined herein.

[0022] The term "cycloalkyl" refers to a hydrocarbon group selected from saturated and partially unsaturated cyclic hydrocarbon groups, e.g., monocyclic and polycyclic (e.g., bicyclic and tricyclic) groups. For example, the cycloalkyl group may be of 3-12, 3-10, 3-8, 3-6,
15 3-4, or 5-6 carbon atoms. Even further for example, the cycloalkyl group may be a monocyclic group of 3-12, 3-8, 3-6, 3-4, or 5-6 carbon atoms. Examples of the monocyclic cycloalkyl group include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, and
20 cyclododecyl groups. Examples of the bicyclic cycloalkyl groups include those having 7-12 ring atoms arranged as a bicycle ring selected from [4,4], [4,5], [5,5], [5,6], and [6,6] ring systems, or as a bridged bicyclic ring selected from bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, and bicyclo[3.2.2]nonane. The ring may be saturated or have at least one double bond (i.e., partially unsaturated), but is not fully conjugated, and is not an aromatic ring, as "aromatic ring" is defined
25 herein.

[0023] The term "heterocyclic" or "heterocycle" or "heterocyclyl" refers to a ring selected from 3- to 12-membered, e.g., 3- to 6-membered, 3- to 5-membered, 4- to 5-membered, or 5- to 6-membered, monocyclic, bicyclic, and tricyclic, saturated and partially unsaturated rings comprising at least one carbon atom in addition to 1, 2, 3, or 4 heteroatoms, selected from,
30 e.g., oxygen, sulfur, nitrogen, and silicon. "Heterocycle" also refers to a 5- to 7-membered heterocyclic ring comprising at least one heteroatom selected from N, O, and S fused with 5-, 6-, and/or 7-membered cycloalkyl, carbocyclic aromatic, or heteroaromatic ring, provided that the

point of attachment is at the heterocyclic ring when the heterocyclic ring is fused with a carbocyclic aromatic or a heteroaromatic ring, and that the point of attachment can be at the cycloalkyl or heterocyclic ring when the heterocyclic ring is fused with cycloalkyl.

[0024] "Heterocycle" also refers to an aliphatic spirocyclic ring comprising at least one heteroatom selected from N, O, and S, provided that the point of attachment is at the heterocyclic ring. The rings may be saturated or have at least one double bond (i.e., partially unsaturated). A heterocycle may be substituted with oxo. The point of the attachment may be carbon or heteroatom in the heterocyclic ring. A heterocycle is not a heteroaryl as defined herein.

[0025] Examples of heterocycles include, but are not limited to, (as numbered from the linkage position assigned priority 1) 1-pyrrolidinyl, 2-pyrrolidinyl, 2,4-imidazolidinyl, 2,3-pyrazolidinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 2,5-piperazinyl, pyranlyl, 2-morpholinyl, 3-morpholinyl, oxiranyl, aziridinyl, thiranyl, azetidiny, oxetanyl, thietanyl, 1,2-dithietanyl, 1,3-dithietanyl, dihydropyridinyl, tetrahydropyridinyl, thiomorpholinyl, thioxanyl, piperazinyl, homopiperazinyl, homopiperidinyl, azepanyl, oxepanyl, thiepanyl, 1,4-oxathianyl, 1,4-dioxepanyl, 1,4-oxathiepanyl, 1,4-oxaazepanyl, 1,4-dithiepanyl, 1,4-thiazepanyl, 1,4-diazepanyl, 1,4-dithianyl, 1,4-azathianyl, oxazepinyl, diazepinyl, thiazepinyl, dihydrothienyl, dihydropyranlyl, dihydrofuranyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranlyl, tetrahydrothiopyranlyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranlyl, 4H-pyranlyl, 1,4-dioxanyl, 1,3-dioxolanyl, pyrazolinyl, pyrazolidinyl, dithianyl, dithiolanyl, pyrazolidinylimidazolinyl, pyrimidinonyl, 1,1-dioxo-thiomorpholinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl and azabicyclo[2.2.2]hexanyl. Substituted heterocycle also includes ring systems substituted with one or more oxo moieties, such as piperidinyl N-oxide, morpholinyl-N-oxide, 1-oxo-1-thiomorpholinyl, and 1, 1-dioxo-1-thiomorpholinyl.

[0026] The term "fused ring" herein refers to a polycyclic ring system, e.g., a bicyclic or tricyclic ring system, in which two rings share only two ring atoms and one bond in common. Examples of fused rings may comprise a fused bicyclic cycloalkyl ring such as those having from 7 to 12 ring atoms arranged as a bicyclic ring selected from [4,4], [4,5], [5,5], [5,6], and [6,6] ring systems as mentioned above; a fused bicyclic aryl ring such as 7- to 12-membered bicyclic aryl ring systems as mentioned above, a fused tricyclic aryl ring such as 10- to 15-membered tricyclic aryl ring systems mentioned above; a fused bicyclic heteroaryl ring such as 8- to 12-membered bicyclic heteroaryl rings as mentioned above, a fused tricyclic heteroaryl ring

such as 11- to 14-membered tricyclic heteroaryl rings as mentioned above; and a fused bicyclic or tricyclic heterocyclyl ring as mentioned above.

[0027] The term “heteroatom” means one or more of oxygen, sulfur, nitrogen, phosphorus, and silicon, including, any oxidized form of nitrogen or sulfur; the quaternized
5 form of any basic nitrogen or a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (wherein R is, e.g., an optionally substituted alkyl group) (as in N-substituted pyrrolidinyl).

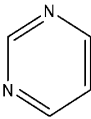
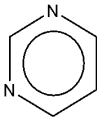
[0028] The term “unsaturated”, as used herein, means that a moiety has one or more units or degrees of unsaturation. Unsaturation is the state in which not all of the
10 available valence bonds in a compound are satisfied by substituents and thus the compound contains one or more double or triple bonds. A double bond may be depicted as ==== (two solid lines). The depiction of ===== (a solid line and a dashed line), as used herein, denotes a bond that may be a double bond or a single bond.

[0029] The term “alkoxy” as used herein, refers to an alkyl group, as defined
15 above, wherein one carbon of the alkyl group is replaced by an oxygen atom, provided that the oxygen atom is linked between two carbon atoms.

[0030] The term “halogen” includes F, Cl, Br, and I, i.e., fluoro, chloro, bromo, and iodo, respectively.

[0031] As used herein, a “CN,” “cyano” or “nitrile” group refers to $\text{-C}\equiv\text{N}$.

20 [0032] As used herein, an “aromatic ring” refers to a carbocyclic or heterocyclic ring that contains conjugated, planar ring systems with delocalized pi electron orbitals comprised of $[4n+2]$ p orbital electrons, wherein n is an integer of 0 to 6. A “non-aromatic” ring refers to a carbocyclic or heterocyclic that does not meet the requirements set forth above for an aromatic ring, and can be either completely or partially saturated. Non-
25 limiting examples of aromatic rings include aryl and heteroaryl rings that are further defined as follows. An “aromatic ring” may be depicted as a cycle with conjugated double

bonds, such as  , or as a cycle with an inside circle, such as .

[0033] The term “aryl” herein refers to a group selected from: monocyclic carbocyclic aromatic rings, for example, phenyl; bicyclic ring systems such as 7-12 membered, e.g., 9-10
30 membered, bicyclic ring systems wherein at least one ring is carbocyclic and aromatic, selected,

for example, from naphthalene, indane, and 1,2,3,4-tetrahydroquinoline; and tricyclic ring systems such as 10-15 membered tricyclic ring systems wherein at least one ring is carbocyclic and aromatic, for example, fluorene.

[0034] For example, the aryl group may be a 6-membered carbocyclic aromatic ring fused to a 5- to 7-membered cycloalkyl or heterocyclic ring optionally comprising at least one heteroatom selected from N, O, and S, provided that the point of attachment is at the carbocyclic aromatic ring when the carbocyclic aromatic ring is fused with a heterocyclic ring, and the point of attachment can be at the carbocyclic aromatic ring or at the cycloalkyl group when the carbocyclic aromatic ring is fused with a cycloalkyl group. Bivalent radicals formed from substituted benzene derivatives and having the free valences at ring atoms are named as substituted phenylene radicals. Bivalent radicals derived from univalent polycyclic hydrocarbon radicals whose names end in "-yl" by removal of one hydrogen atom from the carbon atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, e.g., a naphthyl group with two points of attachment is termed naphthylidene.

[0035] The term "heteroaryl" refers to a group selected from: 5- to 7-membered, e.g., 5- to 6-membered, aromatic, monocyclic rings comprising 1, 2, 3, or 4 heteroatoms selected from N, O, and S, with the remaining ring atoms being carbon; 8- to 12-membered bicyclic rings comprising 1, 2, 3, or 4 heteroatoms, selected from N, O, and S, with the remaining ring atoms being carbon and wherein at least one ring is aromatic and at least one heteroatom is present in the aromatic ring; and 11- to 14-membered tricyclic rings comprising 1, 2, 3, or 4 heteroatoms, selected from N, O, and S, with the remaining ring atoms being carbon and wherein at least one ring is aromatic and at least one heteroatom is present in an aromatic ring.

[0036] For example, the heteroaryl group may be a 5- to 7-membered heterocyclic aromatic ring fused to a 5- to 7-membered cycloalkyl ring. For such fused, bicyclic heteroaryl ring systems wherein only one of the rings comprises at least one heteroatom, the point of attachment may be at the heteroaromatic ring or at the cycloalkyl ring.

[0037] When the total number of S and O atoms in the heteroaryl group exceeds 1, those heteroatoms are not adjacent to one another. In some embodiments, the total number of S and O atoms in the heteroaryl group is not more than 2. In some embodiments, the total number of S and O atoms in the aromatic heterocycle is not more than 1.

[0038] Examples of the heteroaryl group include, but are not limited to, (as numbered from the linkage position assigned priority 1) pyridyl (such as 2-pyridyl, 3-pyridyl, or 4-pyridyl),

cinnolinyl, pyrazinyl, 2,4-pyrimidinyl, 3,5-pyrimidinyl, 2,4-imidazolyl, imidazopyridinyl, isoxazolyl, oxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, tetrazolyl, thienyl, triazinyl, benzothienyl, furyl, benzofuryl, benzoimidazolyl, indolyl, isoindolyl, indolinyl, phthalazinyl, pyrazinyl, pyridazinyl, pyrrolyl, triazolyl, quinolinyl, isoquinolinyl, pyrazolyl, pyrrolopyridinyl
5 (such as 1H-pyrrolo[2,3-b]pyridin-5-yl), pyrazolopyridinyl (such as 1H-pyrazolo[3,4-b]pyridin-5-yl), benzoxazolyl (such as benzo[d]oxazol-6-yl), pteridinyl, purinyl, 1-oxa-2,3-diazolyl, 1-oxa-2,4-diazolyl, 1-oxa-2,5-diazolyl, 1-oxa-3,4-diazolyl, 1-thia-2,3-diazolyl, 1-thia-2,4-diazolyl, 1-thia-2,5-diazolyl, 1-thia-3,4-diazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalyl, naphthyridinyl, furopyridinyl,
10 benzothiazolyl (such as benzo[d]thiazol-6-yl), indazolyl (such as 1H-indazol-5-yl) and 5,6,7,8-tetrahydroisoquinolinyl.

[0039] The term “acyl” refers to a substituent group where a point of attachment in the substituent group is a carbonyl. Exemplary acyl groups include, but are not limited to, -C(=O)R', -C(=O)NR'R'', or -C(=O)OR', wherein R' and R'' are independently selected from
15 hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl, any of which may be further substituted by one or more substituents.

[0040] Some of the compounds may exist with different points of attachment of hydrogen, referred to as “tautomers.” For example, compounds including carbonyl -CH₂C(O)- groups (keto forms) may undergo tautomerism to form hydroxyl -CH=C(OH)- groups (enol
20 forms). Both keto and enol forms, individually as well as mixtures thereof, are also intended to be included where applicable.

[0041] The compounds, tautomers, solvates, or pharmaceutically acceptable salts of the disclosure may contain an asymmetric center and may thus exist as enantiomers. For example, where the compounds possess two or more asymmetric centers, they may additionally exist as
25 diastereoisomers. Enantiomers and diastereoisomers fall within the broader class of stereoisomers. All such possible stereoisomers as substantially pure resolved enantiomers, racemic mixtures thereof, as well as mixtures of diastereoisomers are intended to be included in this disclosure. All stereoisomers of the compounds, tautomers, solvates, and pharmaceutically acceptable salts thereof are intended to be included. Unless specifically mentioned otherwise,
30 reference to one isomer applies to any of the possible isomers. Whenever the isomeric composition is unspecified, all possible isomers are included.

[0042] Diastereomeric mixtures can be separated into their individual

diastereoisomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral
5 alcohol or Mosher's acid chloride), separating the diastereoisomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Enantiomers can also be separated by use of a chiral HPLC column.

[0043] A single stereoisomer, e.g., a substantially pure enantiomer, may be obtained by resolution of the racemic mixture using a method such as formation of diastereoisomers using
10 optically active resolving agents. Racemic mixtures of chiral compounds of the disclosure can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereoisomers, and conversion to the pure stereoisomers, and (3) separation
15 of the substantially pure or enriched stereoisomers directly under chiral conditions.

[0044] The term "substantially pure" in the context of stereoisomers means that the target stereoisomer contains no more than 35%, such as no more than 30%, further such as no more than 25%, even further such as no more than 20%, by weight of any other stereoisomer(s). In some embodiments, the term "substantially pure" means that the target stereoisomer contains
20 no more than 10%, for example, no more than 5%, such as no more than 1%, by weight of any other stereoisomer(s).

[0045] Unless otherwise indicated, structures depicted herein are meant to include all isomeric forms of the structure, e.g., racemic mixtures, cis/trans isomers, geometric (or conformational) isomers, such as (*Z*) and (*E*) double bond isomers, and (*Z*)
25 and (*E*) conformational isomers. Therefore, geometric and conformational mixtures of the compounds disclosed herein are within the scope of the disclosure. Unless otherwise stated, all tautomeric forms of the compounds of the disclosure are within the scope of the disclosure.

[0046] The disclosure provides pharmaceutically acceptable salts of the disclosed
30 compounds, tautomers, solvates, and stereoisomers. A salt of a compound is formed between an acid and a basic group of the compound, such as an amino functional group, or a base and an acidic group of the compound, such as a carboxyl functional group.

[0047] The term “pharmaceutically acceptable,” as used herein, refers to a component that is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and other mammals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A
5 “pharmaceutically acceptable salt” means any non-toxic salt that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this disclosure.

[0048] “Pharmaceutically acceptable salts” include, but are not limited to salts with inorganic acids, selected, for example, from hydrochlorates, phosphates, diphosphates,
10 hydrobromates, sulfates, sulfinates, and nitrates; as well as salts with organic acids, selected, for example, from malates, maleates, fumarates, tartrates, succinates, citrates, lactates, methanesulfonates, p-toluenesulfonates, 2-hydroxyethylsulfonates, benzoates, salicylates, stearates, alkanoates such as acetate, and salts with $\text{HOOC}-(\text{CH}_2)_n\text{-COOH}$, wherein n is selected from 0 to 4. Similarly, examples of pharmaceutically acceptable cations include, but are not
15 limited to, sodium, potassium, calcium, magnesium, aluminum, lithium, and ammonium. Suitable pharmaceutically acceptable salts are, for example, those disclosed in S. M. Berge, *et al. J. Pharmaceutical Sciences*, 1977, 66, pp. 1 to 19.

[0049] Acids commonly employed to form pharmaceutically acceptable salts include inorganic acids such as hydrogen bisulfide, hydrochloric acid, hydrobromic acid,
20 hydroiodic acid, sulfuric acid, and phosphoric acid, as well as organic acids such as para-toluenesulfonic acid, salicylic acid, tartaric acid, bitartaric acid, ascorbic acid, maleic acid, benzenesulfonic acid, fumaric acid, gluconic acid, glucuronic acid, formic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, lactic acid, oxalic acid, para-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid,
25 and acetic acid. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate (i.e., caprate), caprylate, acrylate, formate, isobutyrate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-
30 dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, sulfonate, xylene sulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β -hydroxybutyrate, glycolate, tartrate,

methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate, and other salts. In some embodiments, pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as maleic acid.

5 [0050] Pharmaceutically acceptable salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium, and $N^+(C_{1-4} \text{ alkyl})_4$ salts. This disclosure also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Suitable non-limiting examples of alkali and alkaline earth metal salts include sodium, lithium, potassium, calcium, and magnesium salts. Further non-limiting
10 examples of pharmaceutically acceptable salts include salts of ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate. Other suitable, non-limiting examples of pharmaceutically acceptable salts include besylate and glucosamine salts.

15 [0051] If a compound is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid addition salt. Conversely, if the product is a free base, an addition salt, such as 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. Those
20 skilled in the art will recognize various synthetic methodologies that may be used without undue experimentation to prepare non-toxic pharmaceutically acceptable addition salts.

 [0052] The compounds, tautomers, solvates, stereoisomers, and pharmaceutically acceptable salts of the disclosure may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, $-CD_3$, $-CD_2H$ or $-CDH_2$
25 contains one or more deuteriums in place of hydrogen. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I), or carbon-14 (^{14}C). All isotopic variations of the compounds of the disclosure, whether radioactive or not, are intended to be encompassed within the scope of the disclosure.

 [0053] As used herein, “optionally substituted” is interchangeable with the phrase
30 “substituted or unsubstituted.” In general, the term “substituted,” refers to the replacement of a hydrogen radical in a given structure with the radical of a specified substituent. Unless otherwise indicated, an “optionally substituted” group may have a substituent at each

substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent chosen from a specified group, the substituent may be either the same or different at every position.

[0054] Combinations of chemical components, e.g., substituents, ring structures, linkers, and/or heteroatoms, envisioned by this disclosure are those that result in the formation of stable or chemically feasible compounds.

[0055] In some embodiments, substituents are independently selected from optionally substituted heteroatom and optionally substituted, optionally hetero-, optionally cyclic C₁-C₁₈ hydrocarbyl, particularly wherein the optionally substituted, optionally hetero-, optionally cyclic C₁-C₁₈ hydrocarbyl is optionally-substituted, optionally hetero-, optionally cyclic alkyl, alkenyl or alkynyl, or optionally-substituted, optionally hetero-, aryl; and/or the optionally substituted heteroatom is halogen, optionally substituted hydroxyl (such as alkoxy, aryloxy), optionally substituted acyl (such as formyl, alkanoyl, carbamoyl, carboxyl, amido), optionally substituted amino (such as amino, alkylamino, dialkylamino, amido, sulfamidyl), optionally substituted thiol (such as mercapto, alkylthiol, aryl thiol), optionally substituted sulfinyl or sulfonyl (such as alkylsulfinyl, arylsulfinyl, alkyl sulfonyl, arylsulfonyl), nitro, or cyano.

[0056] In some embodiments, substituents are independently selected from: halogen, -R', -OR', =O, =NR', =N-OR', -NR'R'', -SR', -SiR'R''R''', -OC(=O)R', -C(=O)R', -CO₂R', -C(=O)NR'R'', -OC(=O)NR'R'', -NR'C(=O)R', -NR'-C(=O)NR''R''', -NR'-SO₂NR''R''', -NR''CO₂R', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -SO₂R', -SO₂NR''R'', -NR''SO₂R, -CN, -NO₂, -N₃, -CH(Ph)₂, perfluoro(C₁-C₄)alkoxy, and perfluoro(C₁-C₄)alkyl, in a number ranging from zero to three, with those groups having zero, one, or two substituents being particularly preferred. R', R'', and R''' each independently refer to hydrogen, unsubstituted C₁-C₈ alkyl and heteroalkyl, C₁-C₈ alkyl and heteroalkyl substituted with one to three halogens, unsubstituted aryl, aryl substituted with one to three halogens, unsubstituted alkyl, alkoxy, or thioalkoxy groups, or aryl-(C₁-C₄) alkyl groups. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6- or 7-membered ring. Hence, -NR'R'' includes 1-pyrrolidinyl and 4-morpholinyl. When the aryl group is 1,2,3,4-tetrahydronaphthalenyl, it may be substituted with a substituted or unsubstituted C₃-C₇ spirocycloalkyl group. The C₃-C₇ spirocycloalkyl group may be substituted in the same manner as defined herein for "cycloalkyl."

[0057] In some embodiments, substituents are selected from: halogen, -R', -OR', =O,

-NR'R", -SR', -SiR'R"R"', -OC(=O)R', -C(=O)R', -CO₂R', -C(=O)NR'R", -OC(=O)NR'R", -NR"C(=O)R', -NR"CO₂R', -NR'-SO₂NR"R"', -S(=O)R', -SO₂R', -SO₂NR'R", -NR"SO₂R', -CN, -NO₂, perfluoro C₁-C₄ alkoxy and perfluoro C₁-C₄ alkyl, where R' and R" are as defined above.

[0058] In some embodiments, substituents are independently selected from substituted or unsubstituted heteroatom, substituted or unsubstituted, 0-3 heteroatom-containing C₁-C₆ alkyl (e.g., C₁-C₃ alkyl or C₁-C₂ alkyl), substituted or unsubstituted, 0-3 heteroatom-containing C₂-C₆ alkenyl (e.g., C₂-C₄ alkenyl), substituted or unsubstituted, 0-3 heteroatom-containing C₂-C₆ alkynyl (e.g., C₂-C₄ alkynyl), or substituted or unsubstituted, 0-3 heteroatom-containing C₆-C₁₄ aryl (e.g., C₅-C₆ aryl), wherein each heteroatom is independently oxygen, phosphorus, sulfur, or nitrogen.

[0059] In some embodiments, substituents are independently selected from aldehyde, aldimine, alkanoyloxy, alkoxy, alkoxycarbonyl, alkyloxy, alkyl, alkenyl, alkynyl, amine, azo, halogen, carbamoyl, carbonyl, carboxamido, carboxyl, cyanyl, ester, haloformyl, hydroperoxyl, hydroxyl, imine, isocyanide, isocyanate, N-tert-butoxycarbonyl, nitrate, nitrile, nitrite, nitro, nitroso, phosphate, phosphono, sulfide, sulfonyl, sulfo, sulfhydryl, thiol, thiocyanyl, trifluoromethyl, and trifluoromethyl ether (OCF₃) groups.

[0060] Preferred substituents are disclosed herein and exemplified in the tables, structures, examples, and claims, and may be applied across different compounds of this disclosure. For example, substituents of a given compound may be combinatorically used with other compounds.

[0061] It may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps are separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example, reverse-phase and normal phase; size exclusion; ion exchange; high, medium, and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed ("SMB") and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography. One skilled in the art may apply such techniques to achieve a desired separation.

[0062] Non-limiting examples of suitable solvents that may be used in this disclosure include water, methanol (MeOH), ethanol (EtOH), dichloromethane or

methylen chloride (CH_2Cl_2), toluene, acetonitrile (MeCN), dimethylformamide (DMF), dimethyl sulfoxide (DMSO), methyl acetate (MeOAc), ethyl acetate (EtOAc), heptanes, isopropyl acetate (IPAc), *tert*-butyl acetate (*t*-BuOAc), isopropyl alcohol (IPA), tetrahydrofuran (THF), 2-methyl tetrahydrofuran (2-Me THF), methyl ethyl ketone (MEK),
5 *tert*-butanol, diethyl ether (Et_2O), methyl-*tert*-butyl ether (MTBE), 1,4-dioxane, and *N*-methyl pyrrolidone (NMP).

[0063] Non-limiting examples of suitable bases that may be used in this disclosure include 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), potassium *tert*-butoxide (KOtBu), potassium carbonate (K_2CO_3), *N*-methylmorpholine (NMM), triethylamine (Et_3N ;
10 TEA), diisopropyl-ethyl amine (*i*-Pr₂EtN; DIPEA), pyridine, potassium hydroxide (KOH), sodium hydroxide (NaOH), lithium hydroxide (LiOH), and sodium methoxide (NaOMe; NaOCH_3).

[0064] The term “subject” refers to an animal including a human.

[0065] The term “therapeutically effective amount” refers to the amount of a
15 compound that produces a desired effect for which it is administered (*e.g.*, improvement in a disease or condition, lessening the severity of a disease or condition, and/or reducing progression of a disease or condition, *e.g.*, ALS, Parkinson’s disease, multiple sclerosis, traumatic brain injury, diabetic neuropathy, and CIPN. The disease or condition may be caused by axonal degeneration. The exact amount of a therapeutically effective amount will
20 depend on the purpose of the treatment and will be ascertainable by one skilled in the art using known techniques (see, *e.g.*, Lloyd (1999), *The Art, Science and Technology of Pharmaceutical Compounding*).

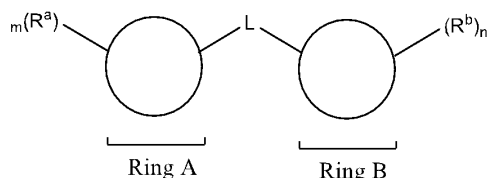
[0066] As used herein, the term “treatment” and its cognates refer to slowing or stopping disease progression. “Treatment” and its cognates as used herein include, but are
25 not limited to the following: complete or partial remission, curing a disease or condition or a symptom thereof, lower risk of a disease or condition, *e.g.*, ALS, Parkinson’s disease, multiple sclerosis, traumatic brain injury, diabetic neuropathy, and CIPN. The disease or condition may be caused by axonal degeneration. Improvements in or lessening the severity of any of these symptoms can be assessed according to methods and techniques known in
30 the art.

[0067] The terms “about” and “approximately,” when used in connection with a number such as a percentage include the number as specified, and a range of the number

(e.g., a range of percentages, for example, a range of $\pm 10\%$ with respect to a specific point value) that is recognized by one of ordinary skill in the art.

II. Compounds and Compositions

[0068] In a 1st embodiment, a compound of this disclosure is a compound of the following structural Formula 1:



Formula 1

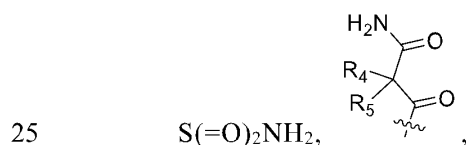
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein:

Ring A is phenyl, a 5- to 10-membered heteroaryl ring, a 5 to 10-membered carbocyclic ring or a 5 to 10-membered heterocyclic ring;

Ring B is phenyl, a 9- to 11-membered aryl ring, a 9- to 11-membered heteroaryl ring, or a 9- to 11-membered heterocyclic ring;

R^a is selected from =O, C₃-C₆ cycloalkyl, -O(C₁-C₄ alkyl), COOH, CN, CONH₂, -C(=O)NH(C₁-C₄ alkyl), -C(=O)N(C₁-C₄ alkyl)₂, -C(=O)O(C₁-C₄ alkyl), halogen, and C₁-C₄ alkyl optionally substituted with 1 to 3 groups selected from halogen, -OH, cyclopropyl, oxetanyl, and azetidiny;

R^b is selected from =O, OH, halogen, CN, -C(=O)NH₂, -C(=O)NH(C₁-C₄ alkyl), -C(=O)O(C₁-C₄ alkyl), optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₃-C₆ heterocyclyl, optionally substituted C₅-C₆ heteroaryl, -O(C₁-C₄ alkyl), -C(=O)(C₁-C₄ alkyl), -C(=O)(optionally substituted C₃-C₆ cycloalkyl), -C(=O)(optionally substituted 5- to 6-membered heterocyclyl), -C(=O)(optionally substituted 5- to 6-membered heteroaryl), -C(=O)(CH₂)_pC(=O)NH₂, -NHC(=O)(C₁-C₄ alkyl), -C(=O)N(C₁-C₄ alkyl)₂, -C(=O)NH(CH₂)_pOH, -



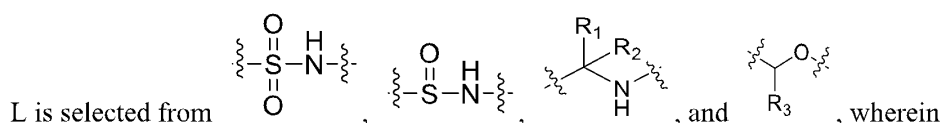
C₁-C₄ alkyl optionally substituted with 1 to 3 groups selected from halogen, NH₂, OH, OCH₃, -C(=O)NH(C₁-C₄ alkyl), -C(=O)O(C₁-C₄ alkyl), -C(=O)N(C₁-C₄ alkyl)₂, -COOH, -C(=O)NH₂, CN, C₃-C₅ cycloalkyl, phenyl, -C(=O)(C₁-C₄ alkyl), -C(=O)(C₃-C₆ cycloalkyl), -C(=O)(5- to 6-membered heterocyclyl), -C(=O)(optionally substituted 5- to 6-membered heteroaryl), C(=O)NH(CH₂)pOH, and 5- to 6-membered heteroaryl,

5- to 6- membered heteroaryl optionally substituted with 1 to 2 groups selected from C₁-C₃ alkyl, =O, -NH₂, -CN, -CONH₂, halogen, and

4- to 6-membered heterocyclyl optionally substituted with 1 to 2 groups selected from =O, -OH, -NH₂, -CN, -CONH₂, halogen, and C₁-C₃ alkyl, or

two R^b attached to the same position on Ring B join to form a C₃-C₆ cycloalkyl,

wherein R₄ and R₅ are each independently selected from H and C₁ to C₃ alkyl or R₄ and R₅ join to form a 3 to 5-membered cycloalkyl;



R₁ is H, D, or C₁-C₆ alkyl, and R₂ is selected from CN, C₁-C₆ alkenyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocyclyl, 5- or 6-membered heteroaryl, phenyl optionally substituted with 1 to 3 groups selected from C₁-C₄ alkyl and halogen, and

C₁-C₆ alkyl optionally substituted with 1 to 3 groups selected from halogen, OH, and phenyl, or

R₁ and R₂ join to form a 3- to 6-membered carbocyclyl or 3- to 6-membered heterocyclyl;

R₃ is C₁-C₄ alkyl optionally substituted with 1 to 3 groups selected from halogen, O(C₁-C₃ alkyl), OH and NH₂;

m is an integer selected from 0, 1, 2, 3, and 4;

n is an integer selected from 0, 1, 2, 3, and 4, and

p is an integer selected from 1, 2, 3, and 4.

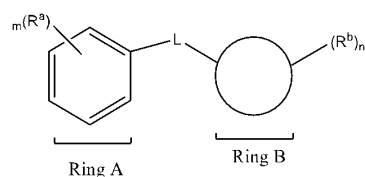
[0069] Combinations of substituents as disclosed herein are those that result in the formation of stable or chemically feasible compounds. For abbreviation or according to common practice, certain hydrogen atoms attached to a certain atom (e.g., a carbon atom C or a nitrogen atom N) are not specifically spelled out in a chemical structure, formula, or notation; hydrogen atoms are deemed to be present to the extent the valences of the certain atom (e.g., C or N) are completed.

[0070] In some embodiments, the compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure is not any of Compounds 1A to 121A.

[0071] In one embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, Ring A is phenyl, pyridinyl, a 5-membered heteroaryl ring comprising one or two heteroatoms selected for O, S and N, or a 6 to 10-membered heterocyclic ring comprising one or two heteroatoms selected from N and O; and all other variables not specifically defined herein are as defined in the preceding embodiments.

[0072] In one embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, Ring B is phenyl, 9- to 11-membered aryl, 9- to 11-membered heteroaryl ring comprising one or two heteroatoms selected from N, S, and O, or a 9- to 11-membered heterocyclyl ring comprising one or two heteroatoms selected from N, S, and O; and all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

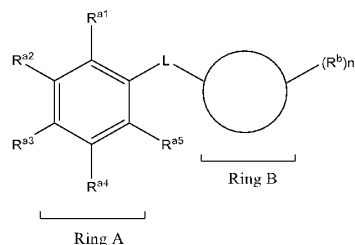
[0073] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 2:



Formula 2

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing; and all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

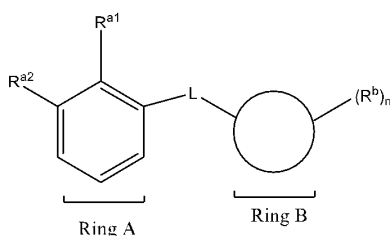
[0074] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 2a:



Formula 2a

5 a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein zero, one, two, three, or four of R^{a1} , R^{a2} , R^{a3} , R^{a4} , and R^{a5} are independently selected from F, Cl, Br, methyl, CF_3 , CF_2H , ethyl, cyclopropyl, and OCH_3 , and the rest of R^{a1} , R^{a2} , R^{a3} , R^{a4} , and R^{a5} are H; and all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

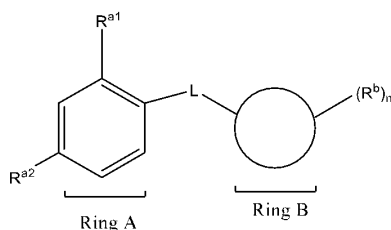
10 [0075] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 2b:



Formula 2b

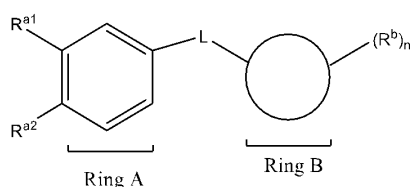
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently selected from F, Cl, Br, methyl, CF_3 , CF_2H , ethyl, and OCH_3 ; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[0076] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 2c:

**Formula 2c**

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently
 5 selected from F, Cl, Br, methyl, CF_3 , CF_2H , ethyl, and OCH_3 ; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[0077] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 2d:

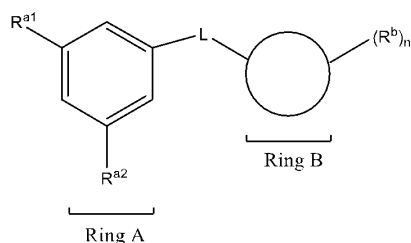


10

Formula 2d

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently
 selected from F, Cl, Br, methyl, CF_3 , CF_2H , ethyl, and OCH_3 ; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

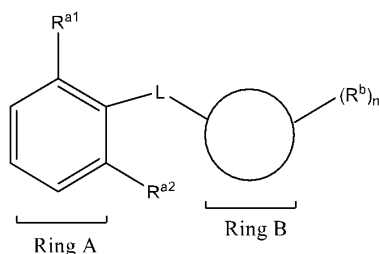
15 [0078] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 2e:

**Formula 2e**

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a
 20 pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently

selected from F, Cl, Br, methyl, CF₃, CF₂H, ethyl, and OCH₃; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[0079] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 2f:



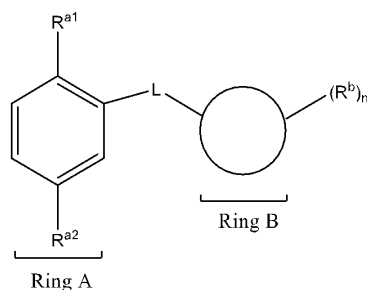
5

Formula 2f

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently selected from F, Cl, Br, methyl, CF₃, CF₂H, ethyl, and OCH₃; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

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[0080] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 2g:

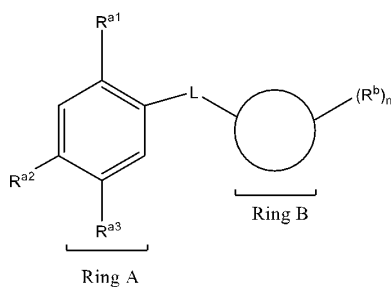


Formula 2g

15 a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently selected from F, Cl, Br, methyl, CF₃, CF₂H, ethyl, and OCH₃; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

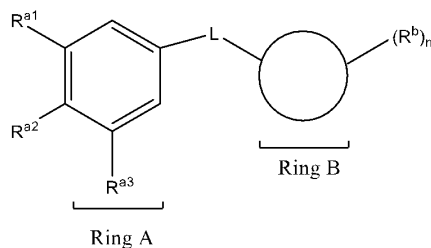
[0081] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 2h:

20

**Formula 2h**

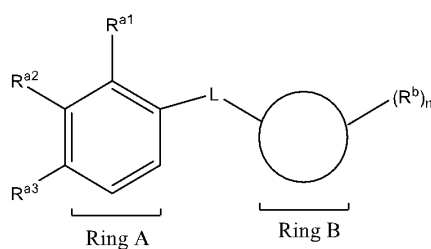
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} , R^{a2} , and R^{a3} are
 5 independently selected from F, Cl, Br, methyl, CF_3 , CF_2H , ethyl, and OCH_3 ; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[0082] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 2i:

**Formula 2i**

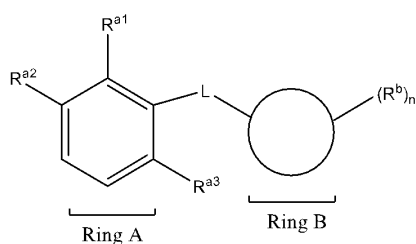
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} , R^{a2} , and R^{a3} are
 15 independently selected from F, Cl, Br, methyl, CF_3 , CF_2H , ethyl, and OCH_3 ; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[0083] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 2j:

**Formula 2j**

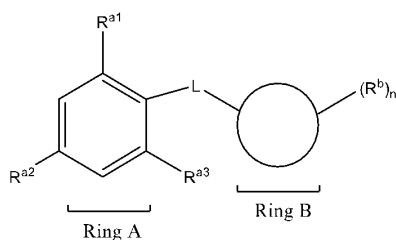
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} , R^{a2} , and R^{a3} are
 5 independently selected from F, Cl, Br, methyl, CF_3 , CF_2H , ethyl, and OCH_3 ; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[0084] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 2k:

**Formula 2k**

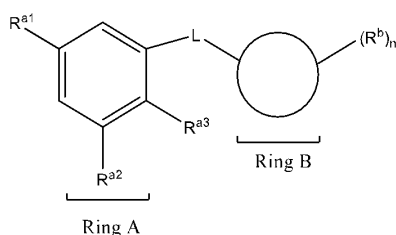
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} , R^{a2} , and R^{a3} are
 15 independently selected from F, Cl, Br, methyl, CF_3 , CF_2H , ethyl, and OCH_3 ; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[0085] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 2L:

**Formula 2L**

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} , R^{a2} , and R^{a3} are
 5 independently selected from F, Cl, Br, methyl, CF_3 , CF_2H , ethyl, and OCH_3 ; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[0086] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 2m:

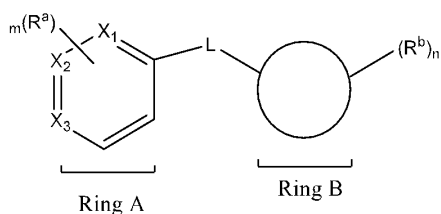


10

Formula 2m

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} , R^{a2} , and R^{a3} are
 15 independently selected from F, Cl, Br, methyl, CF_3 , CF_2H , ethyl, and OCH_3 ; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

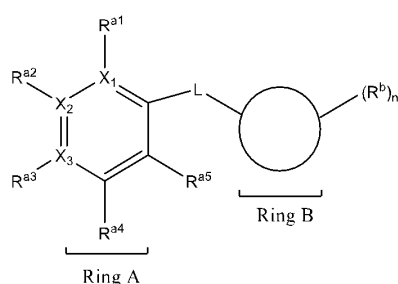
[0087] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 3:



Formula 3

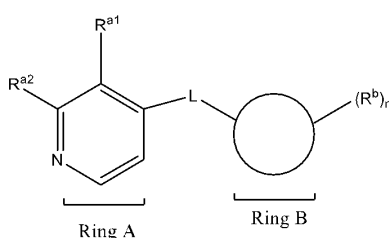
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein one or two of X_1 , X_2 , and X_3 are N and the rest of X_1 , X_2 , and X_3 are C; and all other variables not specifically defined
 5 herein are as defined in any one of the suitable preceding embodiments.

[0088] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 3a:

**Formula 3a**

10 a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein one or two of X_1 , X_2 , and X_3 are N and the rest of X_1 , X_2 , and X_3 are C, zero, one, two, or three of R^{a1} , R^{a2} , R^{a3} , R^{a4} , and R^{a5} are independently selected from F, Cl, Br, methyl, CF_3 , CF_2H , ethyl, cyclopropyl, and OCH_3 , provided that the point of attachment on Ring A is not a N, and the rest of R^{a1} , R^{a2} ,
 15 R^{a3} , R^{a4} , and R^{a5} are H; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

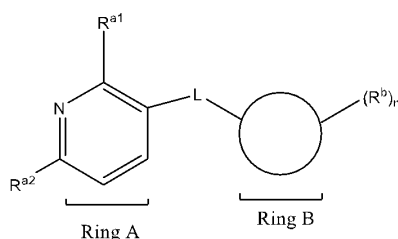
[0089] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 3b:

**Formula 3b**

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently

selected from F, Cl, Br, methyl, CF₃, CF₂H, ethyl, and OCH₃; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

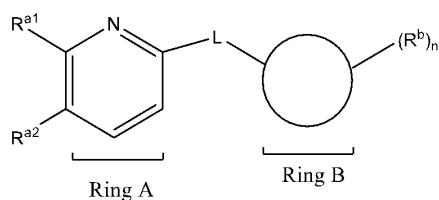
[0090] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 3c:



Formula 3c

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently selected from F, Cl, Br, methyl, CF₃, CF₂H, ethyl, and OCH₃; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

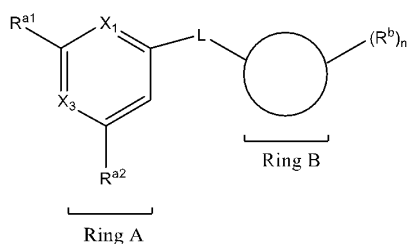
[0091] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 3d:



Formula 3d

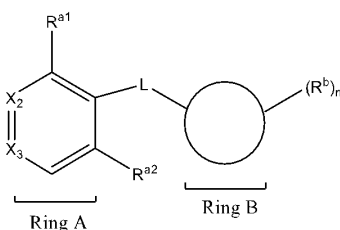
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently selected from F, Cl, Br, methyl, CF₃, CF₂H, ethyl, and OCH₃; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[0092] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 3e:

**Formula 3e**

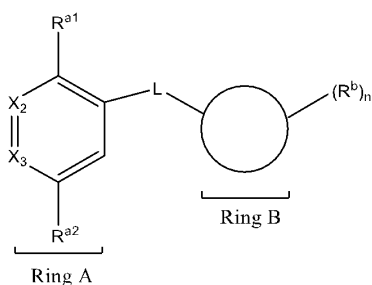
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X_1 and X_3 are independently
 5 selected from C and N, R^{a1} and R^{a2} are independently selected from F, Cl, Br, methyl, CF_3 , CF_2H , ethyl, and OCH_3 ; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[0093] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 3f:

**Formula 3f**

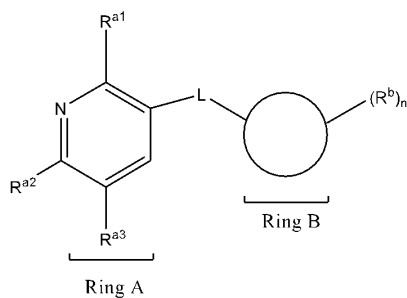
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X_2 and X_3 are independently
 15 selected from C and N, R^{a1} and R^{a2} are independently selected from F, Cl, Br, methyl, CF_3 , CF_2H , ethyl, and OCH_3 ; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[0094] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 3g:

**Formula 3g**

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X_2 and X_3 are independently
 5 selected from C and N, R^{a1} and R^{a2} are independently selected from F, Cl, Br, methyl, CF_3 , CF_2H , ethyl, and OCH_3 ; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[0095] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 3h:

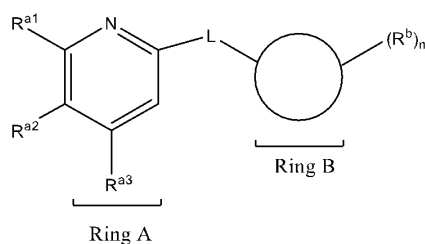


10

Formula 3h

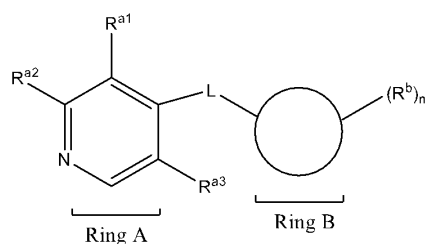
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} , R^{a2} , and R^{a3} are
 15 independently selected from F, Cl, Br, methyl, CF_3 , CF_2H , ethyl, and OCH_3 ; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[0096] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 3i:

**Formula 3i**

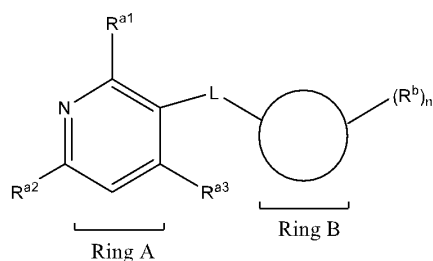
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} , R^{a2} , and R^{a3} are
 5 independently selected from F, Cl, Br, methyl, CF_3 , CF_2H , ethyl, and OCH_3 ; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[0097] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 3j:

**Formula 3j**

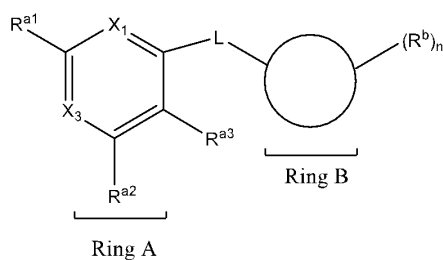
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein one of R^{a1} , R^{a2} , and R^{a3} is
 15 selected from F, Cl, Br, methyl, CF_3 , CF_2H , ethyl, and OCH_3 , the other of them is H; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[0098] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 3k:

**Formula 3k**

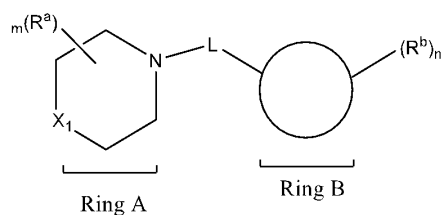
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein one of R^{a1} , R^{a2} , and R^{a3} is
 5 selected from F, Cl, Br, methyl, CF_3 , CF_2H , ethyl, and OCH_3 , the other of them is H; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[0099] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 3L:

**Formula 3L**

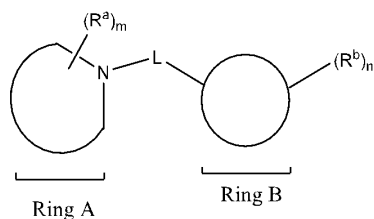
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X_1 and X_3 are independently
 15 selected from C and N, R^{a1} , R^{a2} , and R^{a3} are independently selected from F, Cl, Br, methyl, CF_3 , CF_2H , ethyl, and OCH_3 ; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00100] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 4:

**Formula 4**

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X_1 is selected from C, N, and O; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00101] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 5:

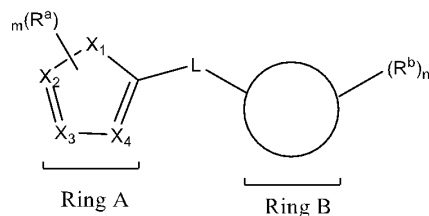
**Formula 5**

10

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein Ring A is an 8-membered, 9-membered, or 10-membered heterocyclic ring, wherein the heterocyclic ring is a fused or bridged ring system; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

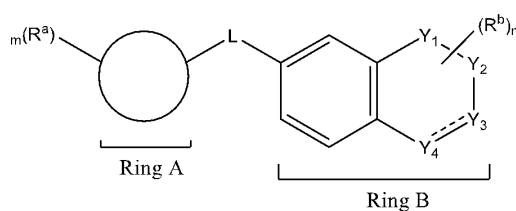
15

[00102] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 6:

**Formula 6**

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein one or two of X_1 , X_2 , X_3 , and X_4 are selected from N, O, and S, and the rest of X_1 , X_2 , X_3 , and X_4 are C; and all other variables not specifically defined herein are as defined in any one of the suitable preceding
5 embodiments.

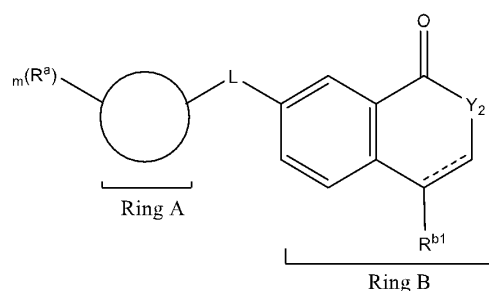
[00103] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 7:



Formula 7

10 a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein zero, one, or two of Y_1 , Y_2 , Y_3 , and Y_4 are N and the rest of Y_1 , Y_2 , Y_3 , and Y_4 are C, R^b is selected from =O, OH, halogen, CN, $-C(=O)NH(C_1-C_4 \text{ alkyl})$, $-C(=O)O(C_1-C_4 \text{ alkyl})$, and C_1-C_4 alkyl optionally substituted with 1 to 2 groups selected from $-C(=O)NH(C_1-C_4 \text{ alkyl})$, $-C(=O)O(C_1-C_4 \text{ alkyl})$, $-C(=O)N(C_1-C_4 \text{ alkyl})_2$, $-C(=O)NH_2$, $-COOH$, and phenyl, and n is 0, 1, and 2; and all other
15 variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00104] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 7a:

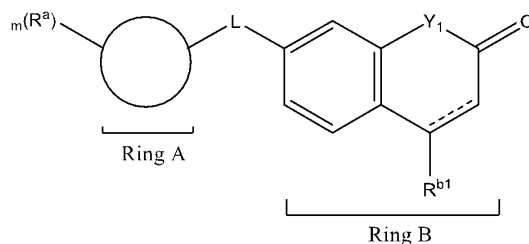


Formula 7a

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a

pharmaceutically acceptable salt of the foregoing, wherein Y_2 is C, N, or O, and R^{b1} is selected from H, halogen, OCH_3 , CN, C_1 to C_3 alkyl, and C_3 to C_5 cycloalkyl; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

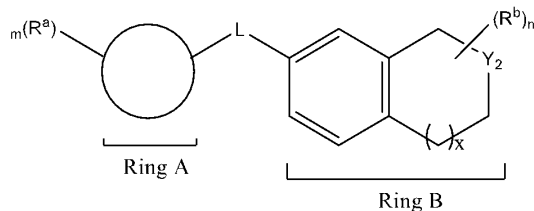
- 5 [00105] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 7b:



Formula 7b

- a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a
10 pharmaceutically acceptable salt of the foregoing, wherein Y_1 is C, N, or O, and R^{b1} is selected from H, halogen, and C_1 to C_3 alkyl; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

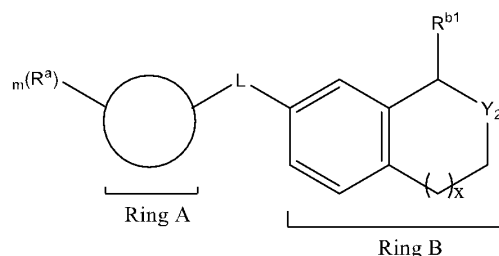
[00106] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 8:



Formula 8

- a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a
pharmaceutically acceptable salt of the foregoing, wherein Y_2 is selected from N, O, and
C, x is 0, 1, and 2, R^b is selected from =O, OH, halogen, CN, $-C(=O)NH(C_1-C_4 \text{ alkyl})$, $-$
20 $C(=O)O(C_1-C_4 \text{ alkyl})$, $-C(=O)N(C_1-C_4 \text{ alkyl})_2$, COOH, and C_1-C_4 alkyl optionally
substituted with 1 to 2 groups selected from $-C(=O)NH(C_1-C_4 \text{ alkyl})$, $-C(=O)O(C_1-C_4$
alkyl), $-C(=O)NH_2$, COOH, and phenyl, and n is 0, 1, and 2; and all other variables not
specifically defined herein are as defined in any one of the suitable preceding embodiments.

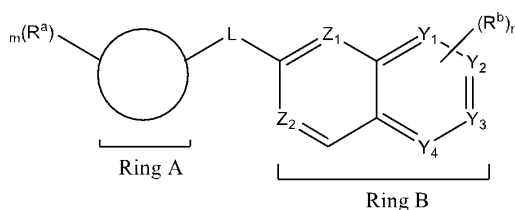
[00107] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 8a:



Formula 8a

5 a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein Y_2 is selected from N, O, and C, x is 0, 1, and 2, and R^{b1} is selected from H, OH, and =O; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

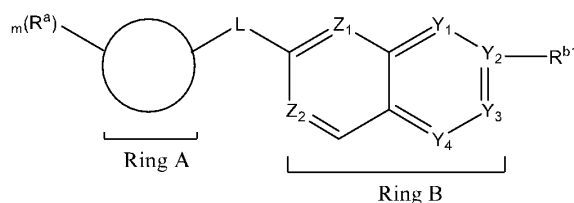
[00108] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 9:



Formula 9

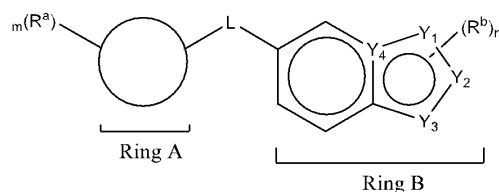
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein zero or one of Y_1 , Y_2 , Y_3 , and Y_4 is N and the rest of Y_1 , Y_2 , Y_3 , and Y_4 are C, zero or one of Z_1 and Z_2 is N and the other is C, R^b is selected from =O, OH, halogen, CN, $-C(=O)NH(C_1-C_4 \text{ alkyl})$, $-C(=O)O(C_1-C_4 \text{ alkyl})$, $-C(=O)N(C_1-C_4 \text{ alkyl})_2$, OCH_3 , and $C_1-C_4 \text{ alkyl}$ optionally substituted with 1 to 2 groups selected from halogen, $-C(=O)NH(C_1-C_4 \text{ alkyl})$, $-C(=O)O(C_1-C_4 \text{ alkyl})$, $-C(=O)NH_2$, and phenyl, and n is 0, 1, and 2; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00109] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 9a:

**Formula 9a**

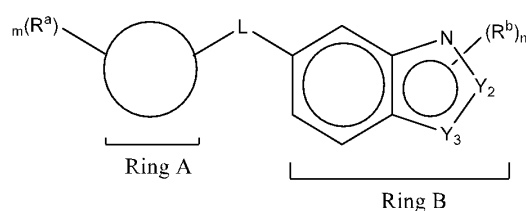
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein zero or one of Y_1 , Y_2 , Y_3 , and Y_4 is N and the rest of Y_1 , Y_2 , Y_3 , and Y_4 are C, zero or one of Z_1 and Z_2 is N and the other is C, R^{b1} is selected from H, halogen, and C_1 to C_3 alkyl, provided that when R^{b1} is not H, Y_2 is C; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00110] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 10:

**Formula 10**

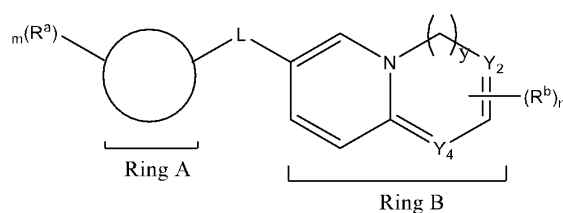
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein zero, one, or two of Y_1 , Y_2 , Y_3 , and Y_4 are N and the rest of Y_1 , Y_2 , Y_3 , and Y_4 are C, R^b is selected from =O, OH, halogen, CN, $-C(=O)NH(C_1-C_4 \text{ alkyl})$, $-C(=O)O(C_1-C_4 \text{ alkyl})$, $-C(=O)N(C_1-C_4 \text{ alkyl})_2$, COOH, C_3-C_5 cycloalkyl, and C_1-C_4 alkyl optionally substituted with 1 to 2 groups selected from $-C(=O)NH(C_1-C_4 \text{ alkyl})$, $-C(=O)O(C_1-C_4 \text{ alkyl})$, $-C(=O)NH_2$, and phenyl, and n is 0, 1, and 2; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00111] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 11:

**Formula 11**

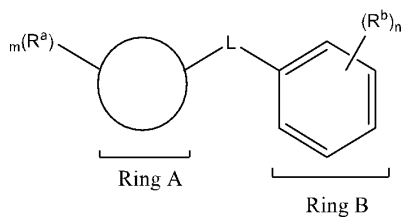
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein one of Y_2 and Y_3 is S or O, and the other is C, R^b is selected from =O, OH, halogen, CN, $-C(=O)NH(C_1-C_4 \text{ alkyl})$, $-C(=O)O(C_1-C_4 \text{ alkyl})$, and C_1-C_4 alkyl optionally substituted with 1 to 2 groups selected from $-C(=O)NH(C_1-C_4 \text{ alkyl})$, $-C(=O)O(C_1-C_4 \text{ alkyl})$, $-C(=O)NH_2$, and phenyl, and n is 0, 1, and 2; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00112] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 12:

**Formula 12**

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein one of Y_2 and Y_4 is N and the other is C, y is 0 or 1, R^b is selected from =O, OH, halogen, CN, $-C(=O)NH(C_1-C_4 \text{ alkyl})$, $-C(=O)O(C_1-C_4 \text{ alkyl})$, and C_1-C_4 alkyl optionally substituted with 1 to 2 groups selected from $-C(=O)NH(C_1-C_4 \text{ alkyl})$, $-C(=O)O(C_1-C_4 \text{ alkyl})$, $-C(=O)NH_2$, and phenyl, and n is 0, 1, and 2; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00113] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 13:

**Formula 13**

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^b is selected from:

- 5 C_1 - C_4 alkyl optionally substituted with 1 to 2 groups selected from $-C(=O)NH(C_1$ - C_4 alkyl), $-C(=O)O(C_1$ - C_4 alkyl), $-C(=O)NH_2$, and phenyl,

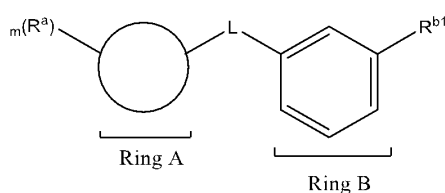
5- to 6- membered heteroaryl optionally substituted with 1 to 2 groups selected from C_1 - C_3 alkyl, and

- 5- to 6-membered heterocyclyl optionally substituted with 1 to 2 groups selected
 10 from $=O$, C_1 - C_3 alkyl, and $O(C_1$ - C_3 alkyl),

and wherein n is 1, and 2;

and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

- [00114] In one embodiment, a compound of the disclosure is a compound of the
 15 following structural Formula 13a:

**Formula 13a**

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{b1} is selected from:

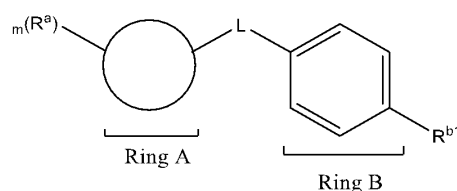
- 20 5- to 6- membered heteroaryl optionally substituted with 1 to 2 groups selected from C_1 - C_3 alkyl and

5- to 6-membered heterocyclyl optionally substituted with 1 to 2 groups selected from $=O$

and C₁-C₃ alkyl;

and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

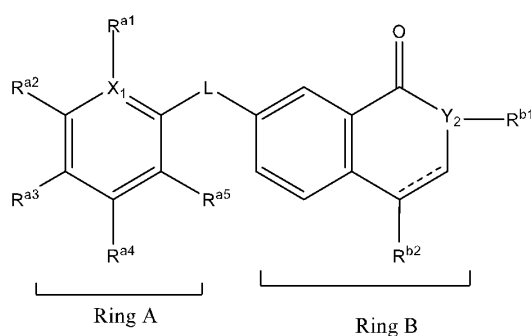
[00115] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 13b:



Formula 13b

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{b1} is selected from C₁-C₄ alkyl optionally substituted with 1 to 2 groups selected from NH₂, -C(=O)NH(C₁-C₄ alkyl), -C(=O)O(C₁-C₄ alkyl), and -C(=O)NH₂; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00116] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 14:

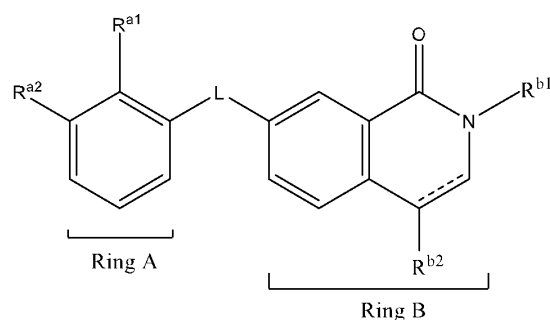


Formula 14

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X₁ is selected from N and C, Y₂ is selected from N and O, wherein zero, one, two, or three of R^{a1}, R^{a2}, R^{a3}, R^{a4}, and R^{a5} are independently selected from F, Cl, Br, methyl, cyclopropyl, and OCH₃, and the rest of R^{a1}, R^{a2}, R^{a3}, R^{a4}, and R^{a5} are H, provided that when X₁ is N, R^{a1} is absent, R^{b1} is selected from H, CH₂CN, and C₁ to C₂ alkyl optionally substituted with C₃-C₄ cycloalkyl provided that

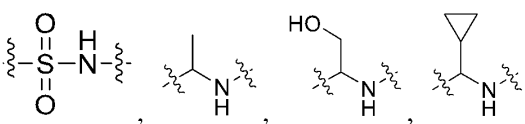
when Y₂ is O, R^{b1} is absent, and R^{b2} is selected from H, halogen, CN, OCH₃, C₁ to C₃ alkyl, and C₃ to C₅ cycloalkyl; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

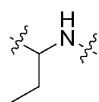
[00117] In a 2nd embodiment, a compound of the disclosure is a compound of the following structural Formula 14a:



Formula 14a

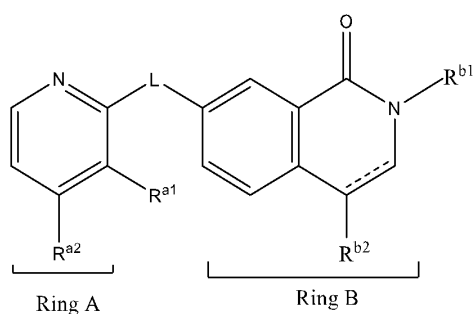
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently selected from F, Cl, Br, methyl, and OCH₃, R^{b1} is selected from H, CH₂CN, and C₁ to C₂ alkyl, R^{b2} is selected from H, halogen, CN, OCH₃, C₁ to C₃ alkyl, and C₃ to C₅

cycloalkyl, and L is selected from  and



; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

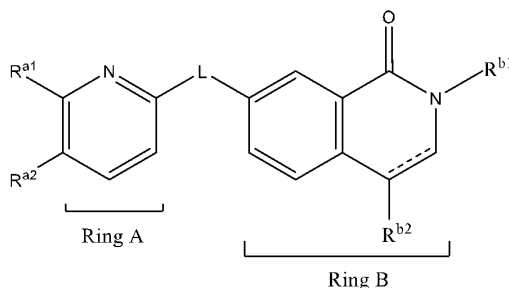
[00118] In a 3rd embodiment, a compound of the disclosure is a compound of the following structural Formula 14b:

**Formula 14b**

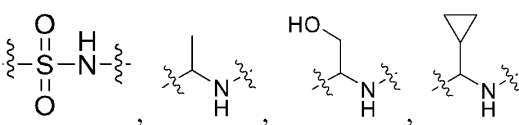
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently
 5 selected from F, Cl, Br, methyl, and OCH_3 , R^{b1} is selected from H and C_1 to C_2 alkyl, R^{b2} is selected from H, halogen, CN, OCH_3 , C_1 to C_3 alkyl, and C_3 to C_5 cycloalkyl, and L is

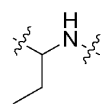
selected from ; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

10 [00119] In a 4th embodiment, a compound of the disclosure is a compound of the following structural Formula 14c:

**Formula 14c**

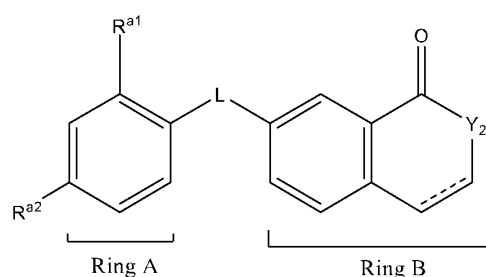
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a
 15 pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently selected from F, Cl, Br, methyl, and OCH_3 , R^{b1} is selected from H and C_1 to C_2 alkyl optionally substituted with C_3 - C_4 cycloalkyl, R^{b2} is selected from H, halogen, and C_1 to

C₃ alkyl, and L is selected from  and



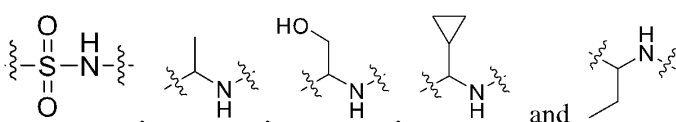
; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00120] In a 5th embodiment, a compound of the disclosure is a compound of the following structural Formula 14d:

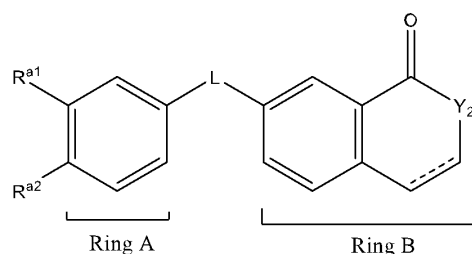


Formula 14d

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently selected from F, Cl, Br, methyl, and OCH₃, Y₂ is selected from N and O, and L is selected

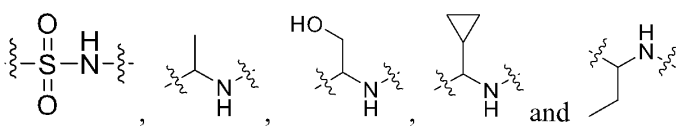
from ; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00121] In a 6th embodiment, a compound of the disclosure is a compound of the following structural Formula 14e:



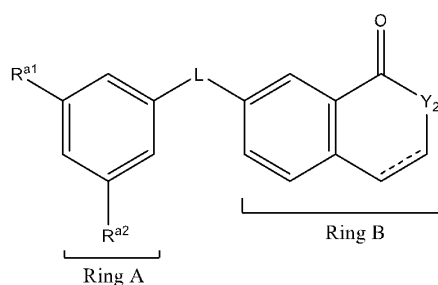
Formula 14e

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently selected from F, Cl, Br, methyl, and OCH_3 , Y_2 is selected from N and O, and L is selected

from ; and all other variables not

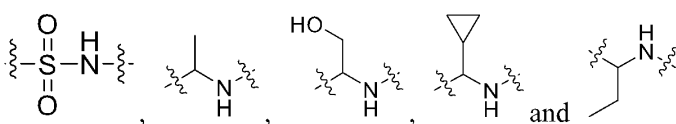
specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00122] In a 7th embodiment, a compound of the disclosure is a compound of the following structural Formula 14f:

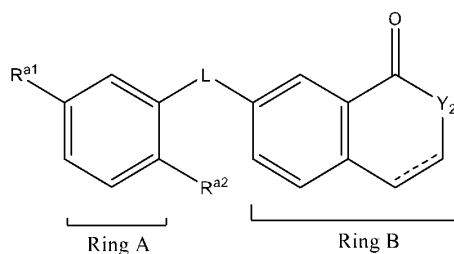


Formula 14f

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently selected from F, Cl, Br, methyl, and OCH_3 , Y_2 is selected from N and O, and L is selected

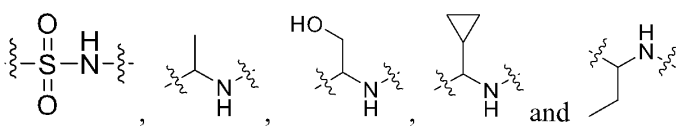
from ; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00123] In a 8th embodiment, a compound of the disclosure is a compound of the following structural Formula 14g:



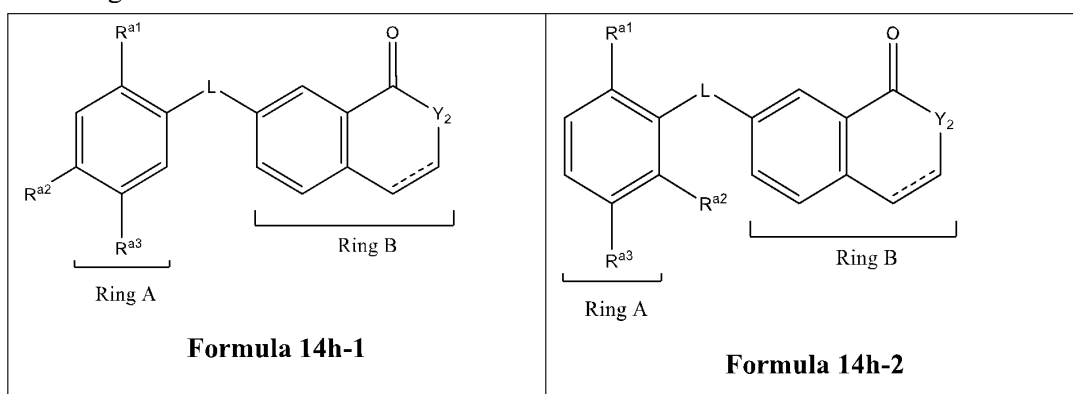
Formula 14g

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently selected from F, Cl, Br, methyl, and OCH_3 , Y_2 is selected from N and O, and L is selected

from ; and all other variables not

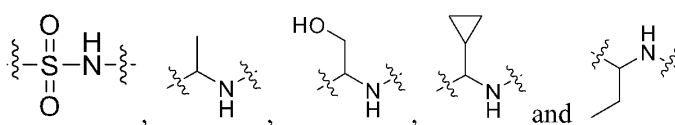
specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00124] In a 9th embodiment, a compound of the disclosure is a compound of the following structural Formula 14h-1 or 14h-2:

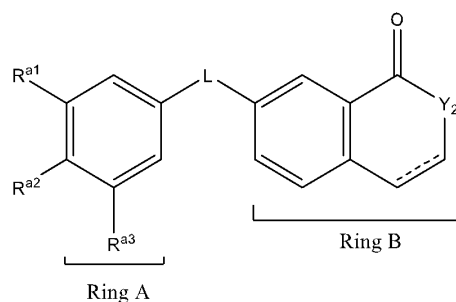


a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} , R^{a2} , and R^{a3} are

independently selected from F, Cl, Br, methyl, and OCH_3 , Y_2 is selected from N and O,

and L is selected from ; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

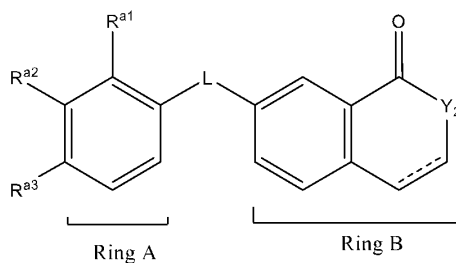
[00125] In a 10th embodiment, a compound of the disclosure is a compound of the following structural Formula 14i:

**Formula 14i**

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} , R^{a2} , and R^{a3} are
 5 independently selected from F, Cl, Br, methyl, and OCH_3 , Y_2 is selected from N and O,

and L is selected from ; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00126] In a 11th embodiment, a compound of the disclosure is a compound of the
 10 following structural Formula 14j:

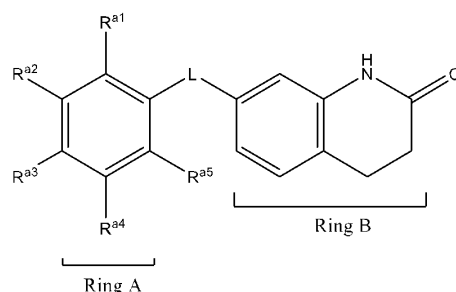
**Formula 14j**

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} , R^{a2} , and R^{a3} are
 15 independently selected from F, Cl, Br, methyl, and OCH_3 , Y_2 is selected from N and O,

and L is selected from ; and all other variables not specifically defined herein are as defined in any one of the suitable

preceding embodiments.

[00127] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 15:



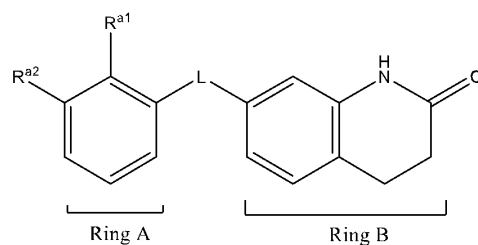
5

Formula 15

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein zero, one, two, or three of R^{a1}, R^{a2}, R^{a3}, R^{a4}, and R^{a5} are independently selected from F, Cl, Br, methyl, and OCH₃, and the rest of R^{a1}, R^{a2}, R^{a3}, R^{a4}, and R^{a5} are H; and all other variables not specifically defined

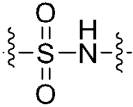
10 herein are as defined in any one of the suitable preceding embodiments.

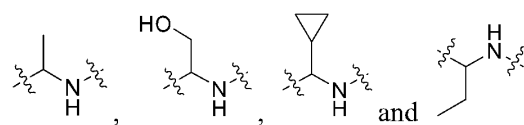
[00128] In a 12th embodiment, a compound of the disclosure is a compound of the following structural Formula 15a:



Formula 15a

15 a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently

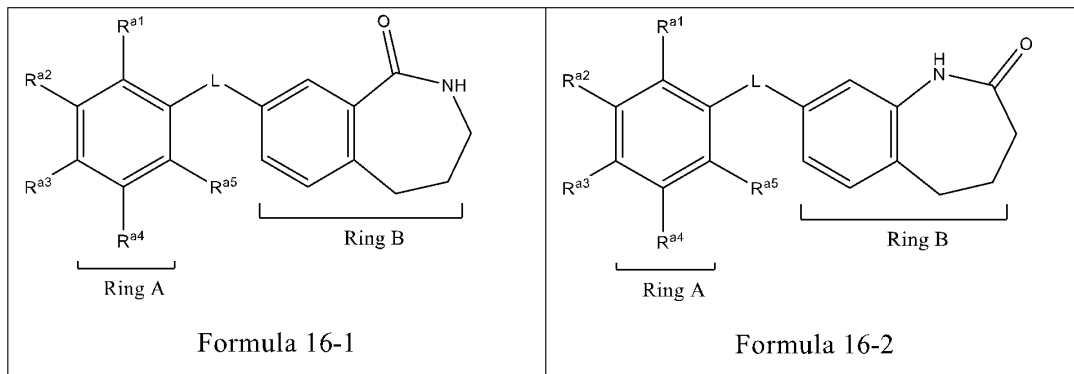
selected from F, Cl, Br, methyl, and OCH₃, and L is selected from ,



; and all other variables not specifically defined

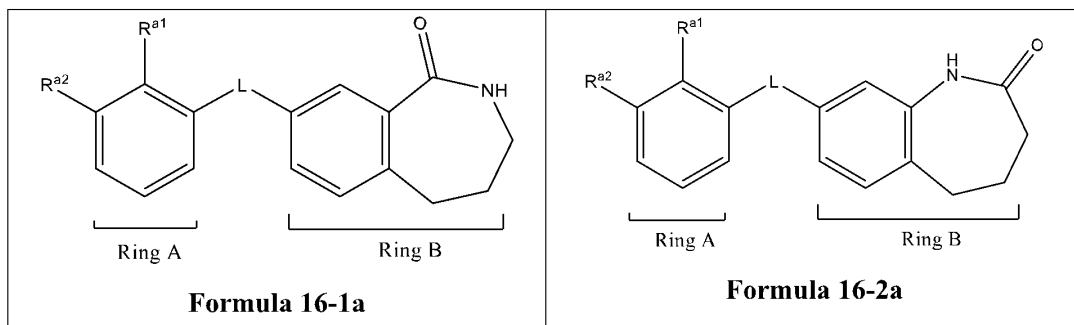
herein are as defined in any one of the suitable preceding embodiments.

[00129] In a 13th embodiment, a compound of the disclosure is a compound of the following structural Formula 16-1 or 16-2:

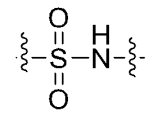


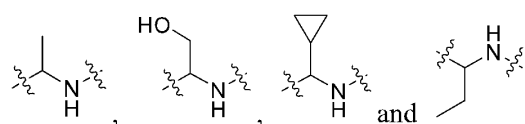
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a
 5 pharmaceutically acceptable salt of the foregoing, wherein zero, one, two, or three of R^{a1}, R^{a2}, R^{a3}, R^{a4}, and R^{a5} are independently selected from F, Cl, Br, methyl, and OCH₃, and the rest of R^{a1}, R^{a2}, R^{a3}, R^{a4}, and R^{a5} are H; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00130] In a 14th embodiment, a compound of the disclosure is a compound of the
 10 following structural Formula 16-1a or 16-2a:



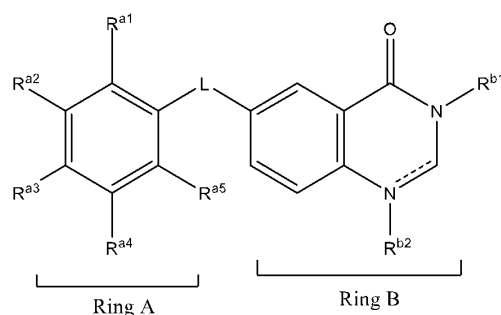
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a
 pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently

selected from F, Cl, Br, methyl, and OCH₃, and L is selected from ,



and all other variables not specifically defined
 15 herein are as defined in any one of the suitable preceding embodiments.

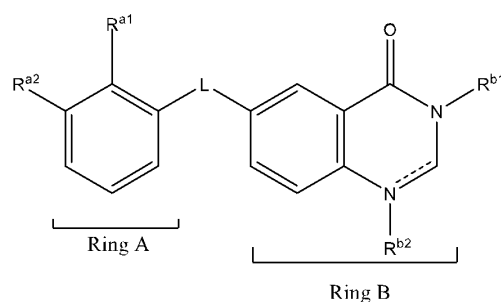
[00131] In a 15th embodiment, a compound of the disclosure is a compound of the following structural Formula 17:



Formula 17

- 5 a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein zero, one, two, or three of R^{a1} , R^{a2} , R^{a3} , R^{a4} , and R^{a5} are independently selected from F, Cl, Br, methyl, and OCH_3 , and the rest of R^{a1} , R^{a2} , R^{a3} , R^{a4} , and R^{a5} are H, R^{b1} is selected from H and C_1 to C_2 alkyl, and R^{b2} is selected from H and C_1 to C_4 alkyl; and all other variables not specifically defined
- 10 herein are as defined in any one of the suitable preceding embodiments.

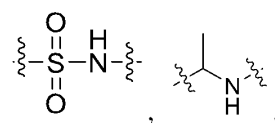
[00132] In a 16th embodiment, a compound of the disclosure is a compound of the following structural Formula 17a:

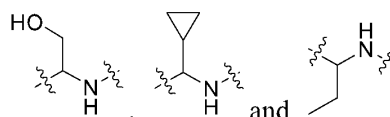


Formula 17a

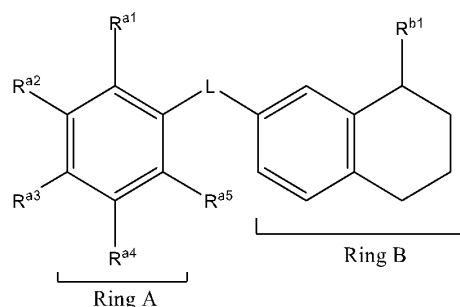
- 15 a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently selected from F, Cl, Br, methyl, and OCH_3 , R^{b1} is selected from H and C_1 to C_2 alkyl, R^{b2}

is selected from H and C_1 to C_4 alkyl, and L is selected from




 ; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00133] In a 17th embodiment, a compound of the disclosure is a compound of the following structural Formula 18:



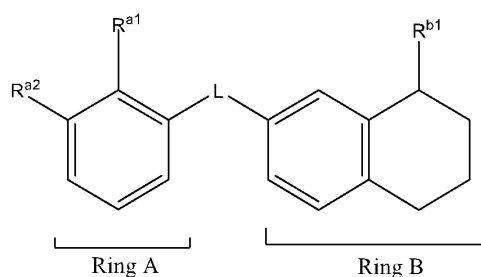
5

Formula 18

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein zero, one, two, or three of R^{a1}, R^{a2}, R^{a3}, R^{a4}, and R^{a5} are independently selected from F, Cl, Br, methyl, and OCH₃, and the rest of R^{a1}, R^{a2}, R^{a3}, R^{a4}, and R^{a5} are H, R^{b1} is selected from =O, -NHCOCH₃, and OH; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

10

[00134] In a 18th embodiment, a compound of the disclosure is a compound of the following structural Formula 18a:

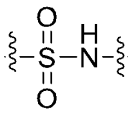
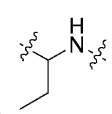


15

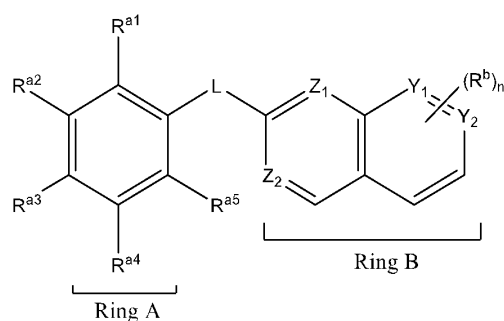
Formula 18a

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently

selected from F, Cl, Br, methyl, and OCH₃, R^{b1} is selected from =O, OH, and -

NHCOCH₃, and L is selected from , , and ; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

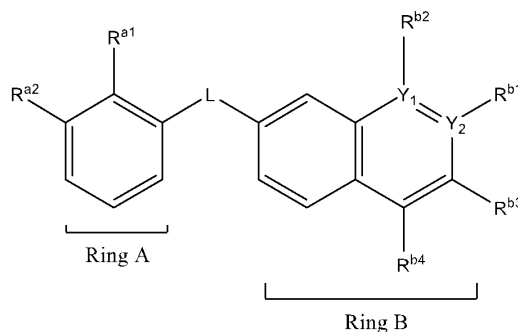
- 5 [00135] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 19:



Formula 19

- a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a
10 pharmaceutically acceptable salt of the foregoing, wherein none or one of Y₁ and Y₂ is N
and the other is C, Z₁ and Z₂ are independently selected from N and C, zero, one, two, or
three of R^{a1}, R^{a2}, R^{a3}, R^{a4}, and R^{a5} are independently selected from F, Cl, Br, methyl, and
OCH₃, and the rest of R^{a1}, R^{a2}, R^{a3}, R^{a4}, and R^{a5} are H; and all other variables not specifically
defined herein are as defined in any one of the suitable preceding embodiments.

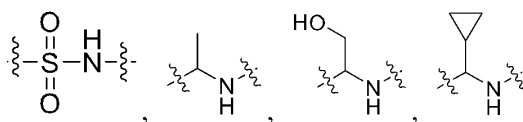
- 15 [00136] In a 19th embodiment, a compound of the disclosure is a compound of the following structural Formula 20:



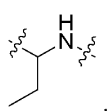
Formula 20

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein none or one of Y_1 and Y_2 is N and the other is C, R^{a1} and R^{a2} are independently selected from F, Cl, Br, methyl, and OCH_3 , R^{b1} is selected from H and C_1 to C_2 alkyl provided that when Y_2 is N, R^{b1} is
 5 absent, R^{b2} is selected from H, CN, C_1 to C_2 alkyl, and $-C(=O)NH_2$, provided that when Y_1 is N, R^{b2} is absent, R^{b3} is selected from H and C_1 to C_2 alkyl, R^{b4} is selected from H

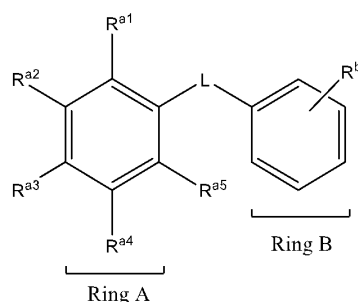
and C_1 to C_2 alkyl, and L is selected from



and



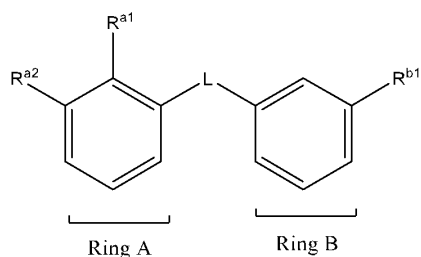
[00137] In one embodiment, a compound of the disclosure is a compound of the
 10 following structural Formula 21:



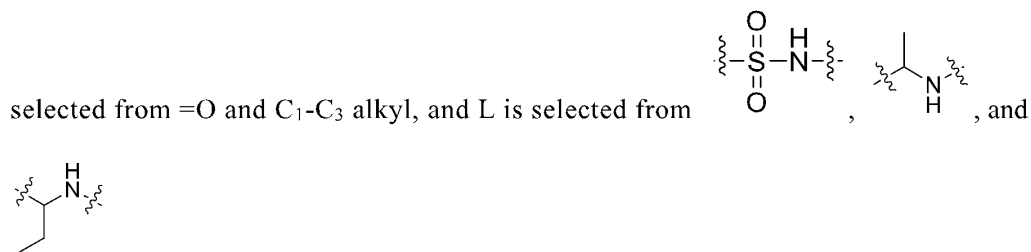
Formula 21

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein zero, one, two, or three of R^{a1} ,
 15 R^{a2} , R^{a3} , R^{a4} , and R^{a5} are independently selected from F, Cl, Br, methyl, and OCH_3 , and the rest of R^{a1} , R^{a2} , R^{a3} , R^{a4} , and R^{a5} are H, R^b is selected from $-C(=O)NH(C_1-C_4 \text{ alkyl})$, $-C(=O)O(C_1-C_4 \text{ alkyl})$, 5- to 6- membered heteroaryl, and 5- to 6-membered heterocyclyl optionally substituted with 1 to 2 groups selected from $=O$ and C_1-C_3 alkyl; and all other variables not specifically defined herein are as defined in any one of the suitable preceding
 20 embodiments.

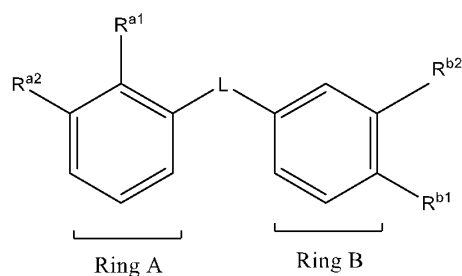
[00138] In a 20th embodiment, a compound of the disclosure is a compound of the following structural Formula 21a:

**Formula 21a**

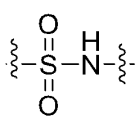
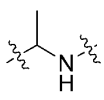
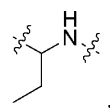
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently
 5 selected from F, Cl, Br, methyl, and OCH_3 , R^{b1} is selected from 5- to 6- membered heteroaryl, and 5- to 6-membered heterocyclyl optionally substituted with 1 to 2 groups



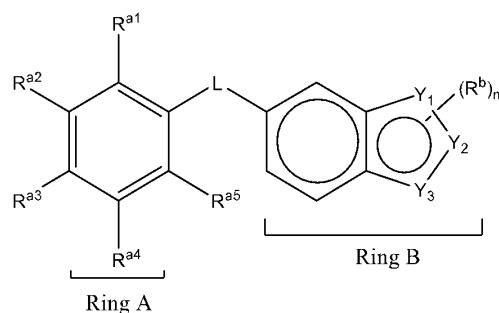
[00139] In a 21st embodiment, a compound of the disclosure is a compound of the
 10 following structural Formula 21b:

**Formula 21b**

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently
 15 selected from F, Cl, Br, methyl, and OCH_3 , R^{b1} is selected from $-C(=O)NH(C_1$ - C_4 alkyl), OCH_3 , and $-C(=O)O(C_1$ - C_4 alkyl), R^{b2} is selected from H and $-C(=O)NH_2$, and L is

selected from , , and .

[00140] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 22:

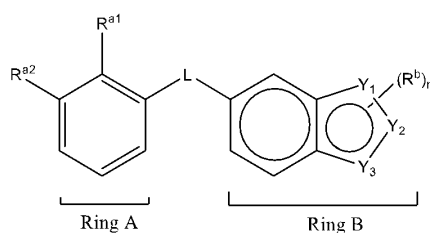


5

Formula 22

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein zero, one, two, or three of R^{a1} , R^{a2} , R^{a3} , R^{a4} , and R^{a5} are independently selected from F, Cl, Br, methyl, and OCH_3 , and the rest of R^{a1} , R^{a2} , R^{a3} , R^{a4} , and R^{a5} are H, zero, one, or two of Y_1 , Y_2 , and Y_3 are N and the
10 rest of Y_1 , Y_2 , and Y_3 are C, R^b is selected from C_1 to C_2 alkyl, C_3 to C_4 cycloalkyl, and halogen, and n is 0, 1, or 2; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00141] In a 22nd embodiment, a compound of the disclosure is a compound of the following structural Formula 22a:

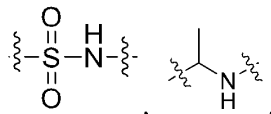
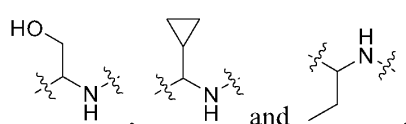
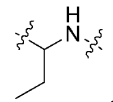


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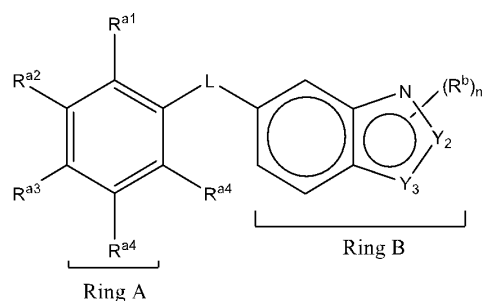
Formula 22a

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently selected from F, Cl, Br, methyl, and OCH_3 , zero, one, or two of Y_1 , Y_2 , and Y_3 are N and

the rest of Y_1 , Y_2 , and Y_3 are C, R^b is selected from C_1 to C_2 alkyl, C_3 to C_5 cycloalkyl,

CN, $C(O)NH_2$, and halogen, n is 0, 1, or 2, and L is selected from , , and .

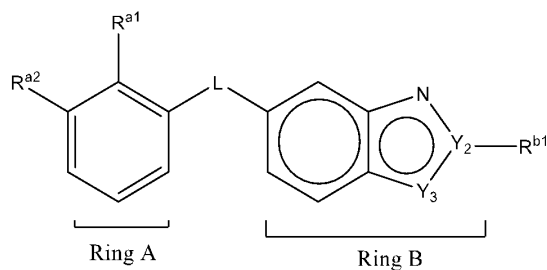
[00142] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 23:



Formula 23

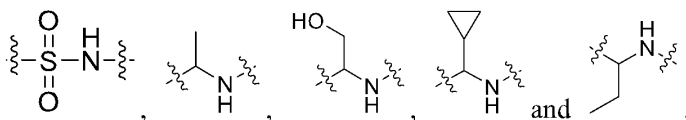
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein zero, one, two, or three of R^{a1} , R^{a2} , R^{a3} , R^{a4} , and R^{a5} are independently selected from F, Cl, Br, methyl, and OCH_3 , and the rest of R^{a1} , R^{a2} , R^{a3} , R^{a4} , and R^{a5} are H, one of Y_2 and Y_3 is S or O, and the other is C; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00143] In a 23rd embodiment, a compound of the disclosure is a compound of the following structural Formula 23a:

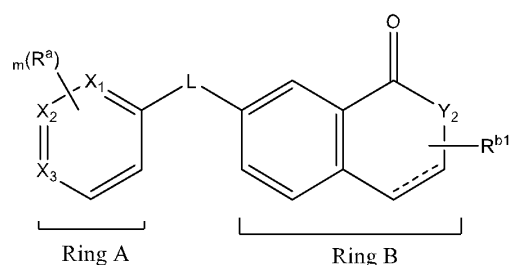


Formula 23a

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently selected from F, Cl, Br, methyl, and OCH_3 , R^{b1} is selected from H, C_1 to C_3 alkyl, halogen, C_3 - C_5 cycloalkyl, CN, and $CONH_2$, provided that when Y_2 is S or O, R^{b1} is
 5 absent, one of Y_2 and Y_3 is S or O, and the other is C, and L is selected from



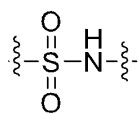
[00144] In a 24th embodiment, a compound of the disclosure is a compound of the following structural Formula 24:



10

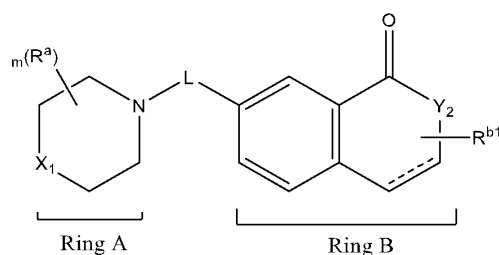
Formula 24

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein one of X_1 , X_2 , and X_3 is N and the other two of them are C, Y_2 is selected from C, N, and O, and R^{b1} is selected from C_1 to C_2 alkyl, C_3 to C_5 cycloalkyl, $O(C_1$ - C_3 alkyl) and halogen; and all other variables not
 15 specifically defined herein are as defined in any one of the suitable preceding embodiments. In



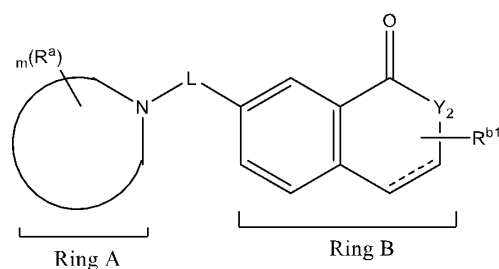
some embodiments, L is

[00145] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 25:

**Formula 25**

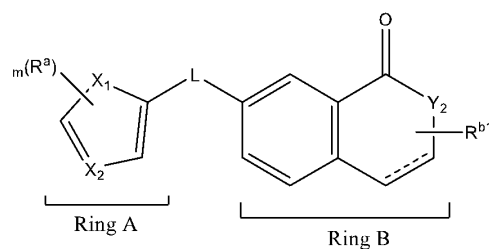
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X_1 is selected from C, N, and O, Y_2 is selected from C, N and O, and R^{b1} is selected from C_1 to C_2 alkyl, C_3 to C_5 cycloalkyl, $O(C_1-C_3$ alkyl), and halogen; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00146] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 26:

**Formula 26**

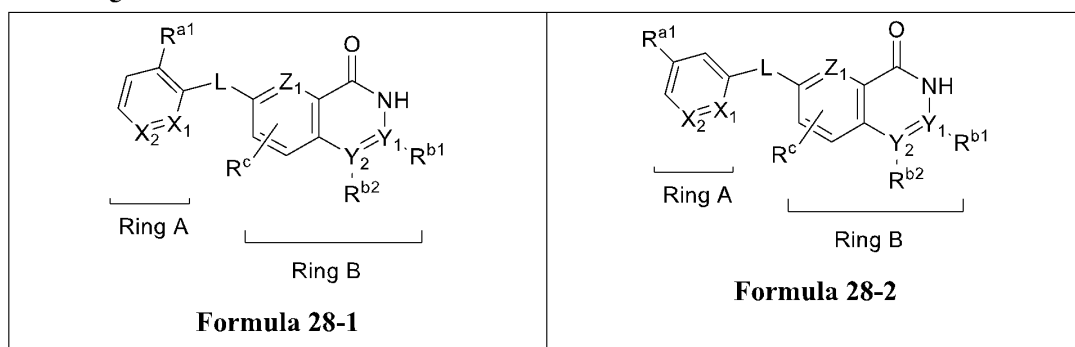
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing wherein Ring A is an 8-membered, 9-membered, or 10-membered heterocyclic ring, wherein the heterocyclic ring is a fused or bridged ring system, Y_2 is selected from C, N, and O, and R^{b1} is selected from C_1 to C_2 alkyl, C_3 to C_5 cycloalkyl, $O(C_1-C_3$ alkyl), and halogen; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00147] In one embodiment, a compound of the disclosure is a compound of the following structural Formula 27:

**Formula 27**

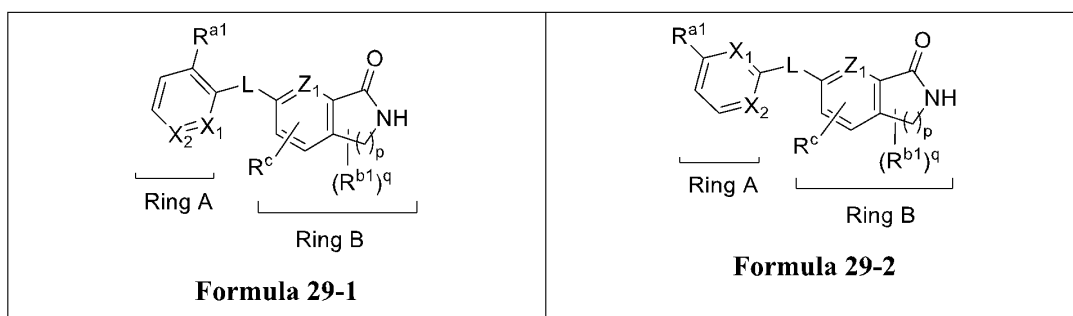
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing wherein X_1 is selected from C, O and S, X_2 is selected from N and C, Y_2 is selected from C, N, and O, and R^{b1} is selected from C_1 to C_2 alkyl and halogen; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00148] In a 25th embodiment, a compound of the disclosure is a compound of the following structural Formula 28-1 or 28-2:



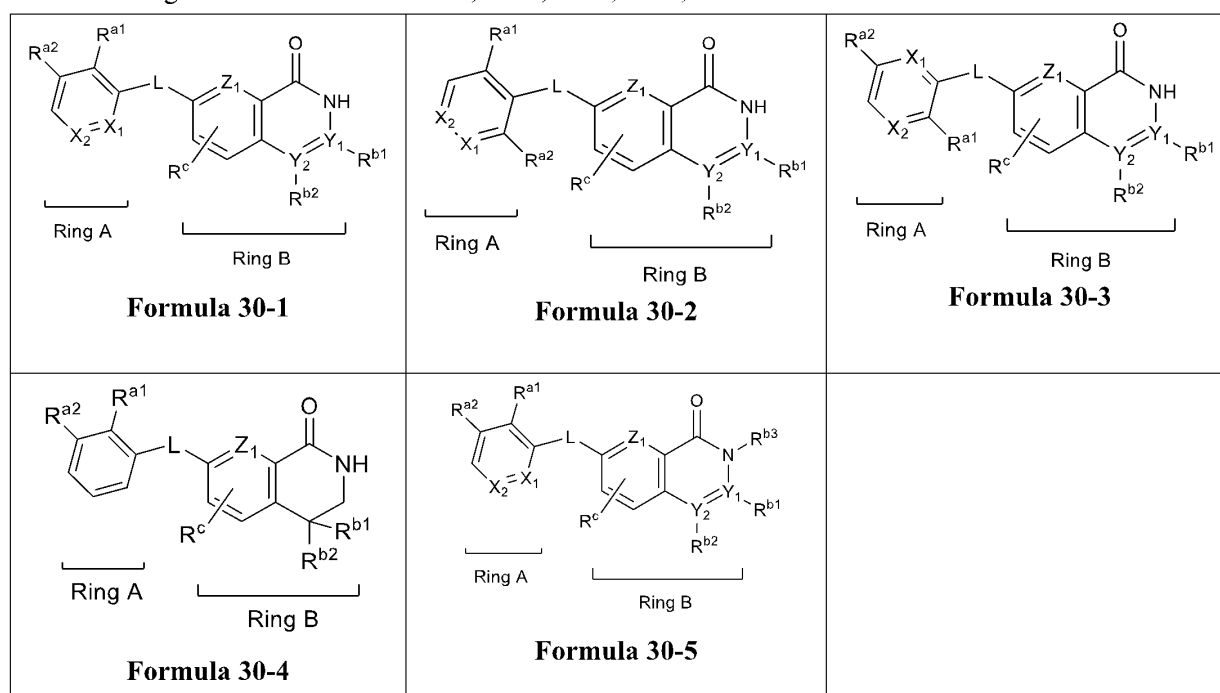
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X_1 , X_2 , Y_1 , Y_2 , and Z_1 are independently selected from C and N, R^{a1} is selected from F, Cl, Br, methyl, CF_3 , CF_2H , CN, $CONH_2$, CH_2NH_2 , ethyl, and cyclopropyl, R^{b1} and R^{b2} are independently selected from H, F, Cl, Br, methyl, CN, CF_3 , CF_2H , ethyl, cyclopropyl, and OCH_3 , wherein R^{b1} and R^{b2} are absent when connected to N in Ring B, and R^c is H, halogen, CN, or methyl; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00149] In a 26th embodiment, a compound of the disclosure is a compound of the following structural Formula 29-1 or 29-2:



a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X_1 , X_2 , and Z_1 are independently selected from C and N, R^{a1} is selected from F, Cl, Br, methyl, CF_3 , CF_2H , CN, $CONH_2$, CH_2NH_2 , ethyl, and cyclopropyl, R^{b1} is selected from F, Cl, Br, methyl, CN, CF_3 , CF_2H , ethyl, CH_2OH , cyclopropyl, and OCH_3 , wherein R^{b1} is absent or C_1 to C_4 alkyl when connected to N in Ring B, R^c is H, halogen, CN, or methyl, p is 1, 2, or 3, and q is 0, 1, or 2; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

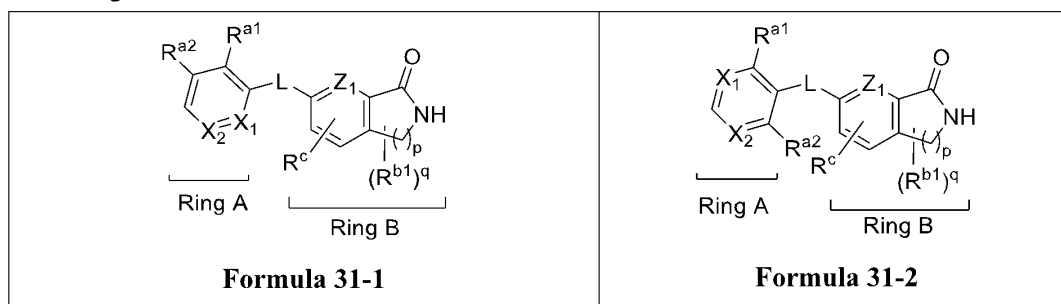
[00150] In a 27th embodiment, a compound of the disclosure is a compound of the following structural Formula 30-1, 30-2, 30-3, 30-4, or 30-5:



a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X_1 , X_2 , Y_1 , Y_2 , and Z_1 are

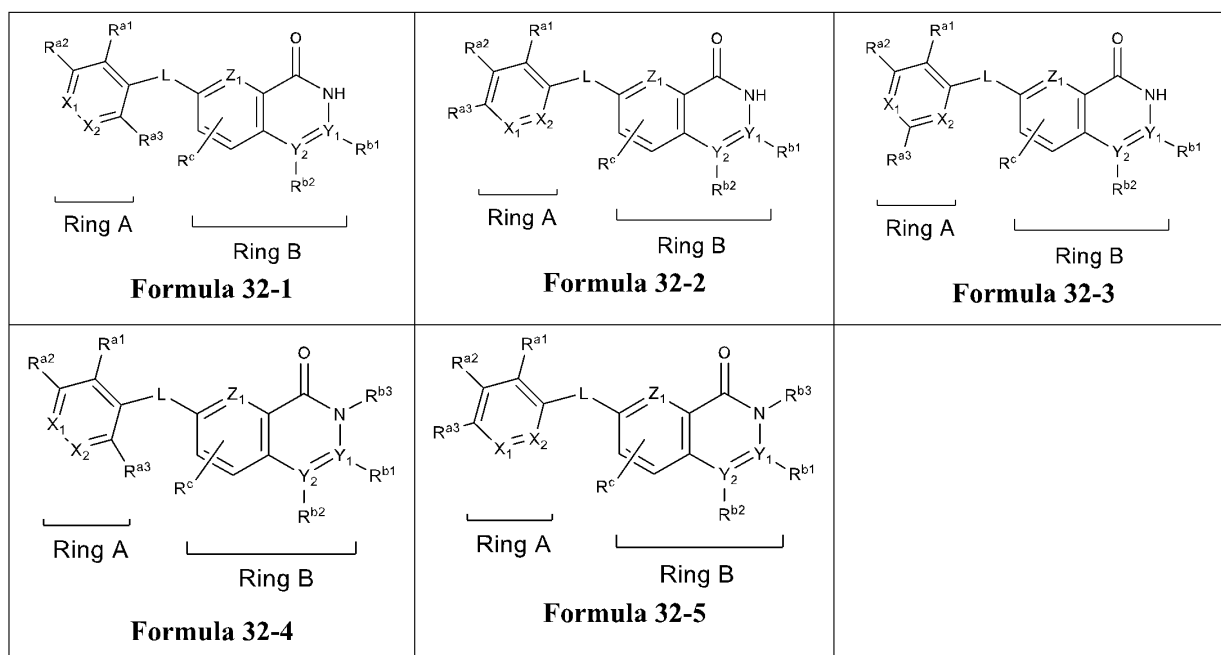
independently selected from C and N, R^{a1} and R^{a2} are each independently selected from F, Cl, Br, methyl, CF_3 , CF_2H , ethyl, CN, $CONH_2$, CH_2NH_2 , and cyclopropyl, R^{b1} and R^{b2} are independently selected from H, F, Cl, Br, methyl, CN, CF_3 , CF_2H , ethyl, cyclopropyl, and OCH_3 , wherein R^{b1} and R^{b2} are absent when connected to N in Ring B, R^{b3} is selected from C_1 to C_4 alkyl optionally substituted with $-C(=O)NH_2$, 3 to 5-membered cycloalkyl optionally substituted with OH, and 5-6 membered heteroaryl optionally substituted with 1-2 groups selected from F, Cl, Br, Me, CF_3 , CF_2H , CN, $CONH_2$, and NH_2 , and R^c is H, halogen, CN, or methyl; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

10 [00151] In a 28th embodiment, a compound of the disclosure is a compound of the following structural Formula 31-1 or 31-2:



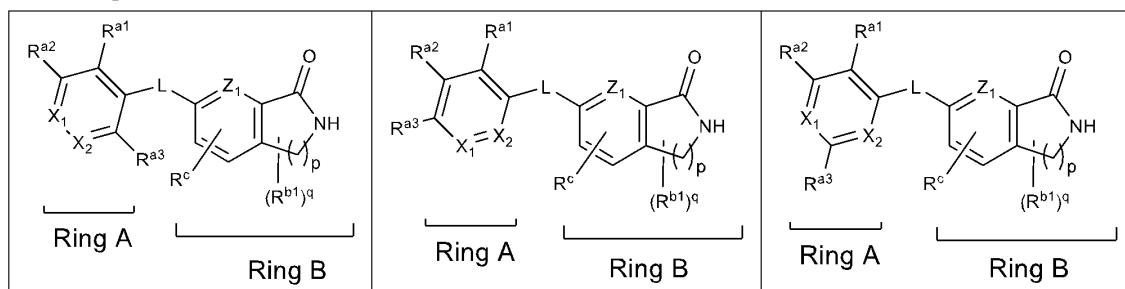
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X_1 , X_2 , and Z_1 are independently selected from C and N, R^{a1} and R^{a2} are each independently selected from F, Cl, Br, methyl, CF_3 , CF_2H , CN, $CONH_2$, CH_2NH_2 , ethyl, and cyclopropyl, R^{b1} is selected from F, Cl, Br, methyl, CN, CF_3 , CF_2H , ethyl, cyclopropyl, and OCH_3 , wherein R^{b1} is absent or C_1 to C_4 alkyl when connected to N in Ring B, R^c is H, halogen, CN, or methyl, p is 1, 2, or 3, and q is 0, 1, or 2; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

20 [00152] In a 29th embodiment, a compound of the disclosure is a compound of the following structural Formula 32-1, 32-2, 32-3, 32-4, or 32-5:



a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X_1 , X_2 , Y_1 , Y_2 , and Z_1 are independently selected from C and N, R^{a1} , R^{a2} , and R^{a3} are each independently selected from F, Cl, Br, methyl, CF_3 , CF_2H , CN, $CONH_2$, CH_2NH_2 , ethyl, cyclopropyl, and OCH_3 , R^{b1} and R^{b2} are independently selected from H, F, Cl, Br, methyl, CN, CF_3 , CF_2H , ethyl, cyclopropyl, and OCH_3 , wherein R^{b1} and R^{b2} are absent when connected to N in Ring B, R^{b3} is selected from H, C_1 to C_4 alkyl optionally substituted with $-C(=O)NH_2$, 3 to 5-membered cycloalkyl optionally substituted with OH, and 5-6 membered heteroaryl optionally substituted with 1-2 groups selected from F, Cl, Br, Me, CF_3 , CF_2H , CN, $CONH_2$, and NH_2 , and R^c is H, halogen, CN, or methyl; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

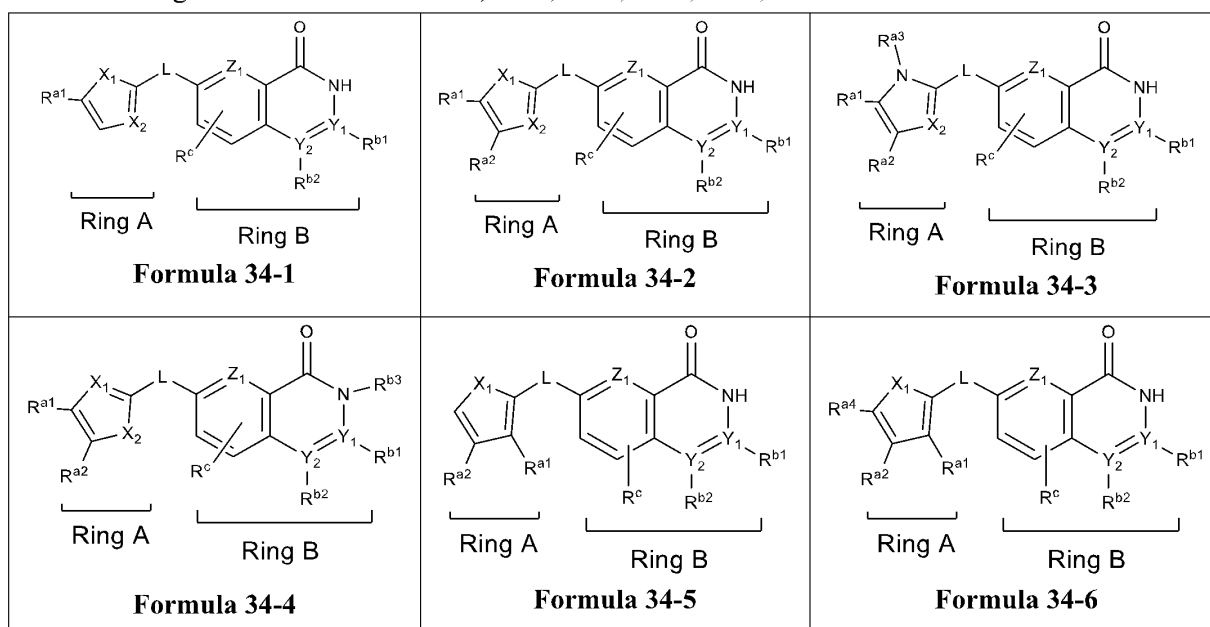
[00153] In a 30th embodiment, a compound of the disclosure is a compound of the following structural Formula 33-1, 33-2, or 33-3:



Formula 33-1	Formula 33-2	Formula 33-3
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a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X_1 , X_2 , and Z_1 are independently selected from C and N, R^{a1} , R^{a2} , and R^{a3} are each independently selected from F, Cl, Br, methyl, CF_3 , CF_2H , CN, $CONH_2$, CH_2NH_2 , ethyl, cyclopropyl, and OCH_3 , R^{b1} is selected from F, Cl, Br, methyl, CN, CF_3 , CF_2H , ethyl, cyclopropyl, and OCH_3 , wherein R^{b1} is absent or C_1 to C_4 alkyl when connected to N in Ring B, and R^c is H, halogen, CN, or methyl, p is 1, 2, or 3, and q is 0, 1, or 2; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

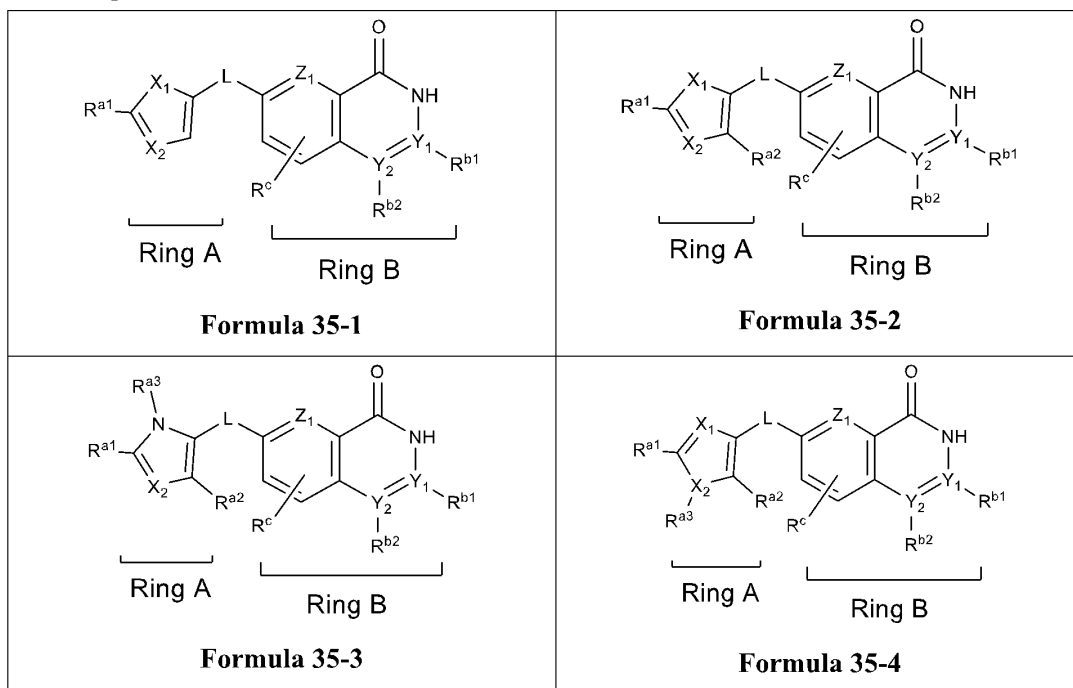
[00154] In a 31st embodiment, a compound of the disclosure is a compound of the following structural Formula 34-1, 34-2, 34-3, 34-4, 34-5, or 34-6:



a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X_1 and X_2 are independently selected from N, O, and S, Y_1 , Y_2 , and Z_1 are independently selected from C and N, R^{a1} and R^{a2} , and R^{a4} are each independently selected from F, Cl, Br, C_1 to C_4 alkyl, CF_3 , CF_2H , CN, $CONH_2$, CH_2NH_2 , and OCH_3 , R^{a3} is C_1 to C_4 alkyl, R^{b1} and R^{b2} are independently selected from H, F, Cl, Br, methyl, CN, CF_3 , CF_2H , ethyl, cyclopropyl, and OCH_3 , wherein R^{b1} and R^{b2} are absent when connected to N in Ring B, R^{b3} is selected from H, 5- to 6-membered heteroaryl optionally substituted with 1-2 groups selected from F, Cl, Br, Me, CF_3 , CF_2H , CN, $CONH_2$, and NH_2 , and C_1 to C_4 alkyl optionally substituted with $-C(=O)NH_2$, and R^c is H, halogen, CN,

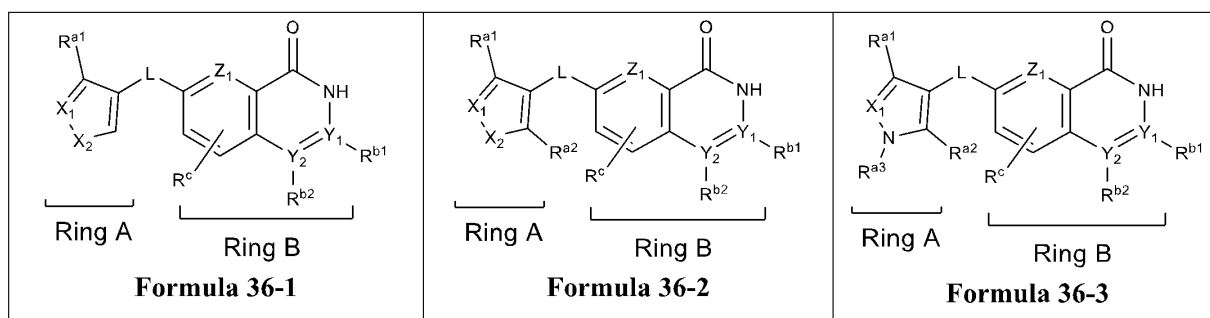
or methyl; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00155] In a 32nd embodiment, a compound of the disclosure is a compound of the following structural Formula 35-1, 35-2, 35-3, or 35-4:



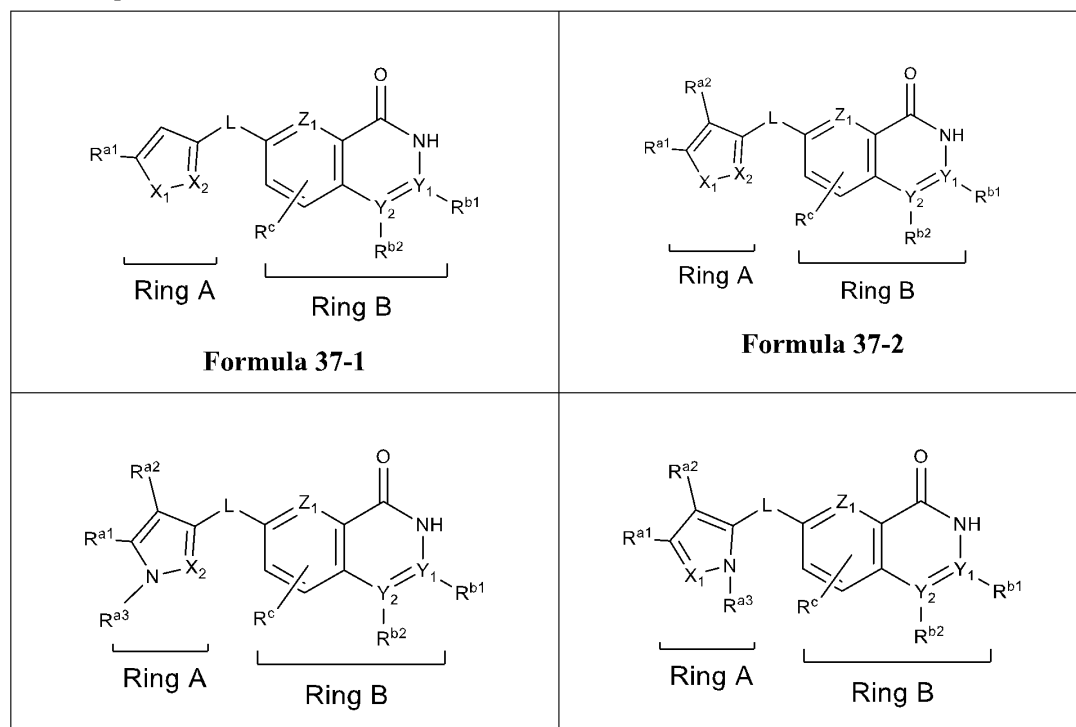
- 5 a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X₁ and X₂ are independently selected from N, O, and S, Y₁, Y₂, and Z₁ are independently selected from C and N, R^{a1} and R^{a2} are each independently selected from F, Cl, Br, C₁ to C₄ alkyl, CF₃, CF₂H, and OCH₃, R^{a3} is C₁ to C₄ alkyl, R^{b1} and R^{b2} are independently selected from H, F, Cl, Br, methyl, CN, CF₃,
 10 CF₂H, ethyl, cyclopropyl, and OCH₃, wherein R^{b1} and R^{b2} are absent when connected to N in Ring B, and R^c is H, halogen, CN, or methyl; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

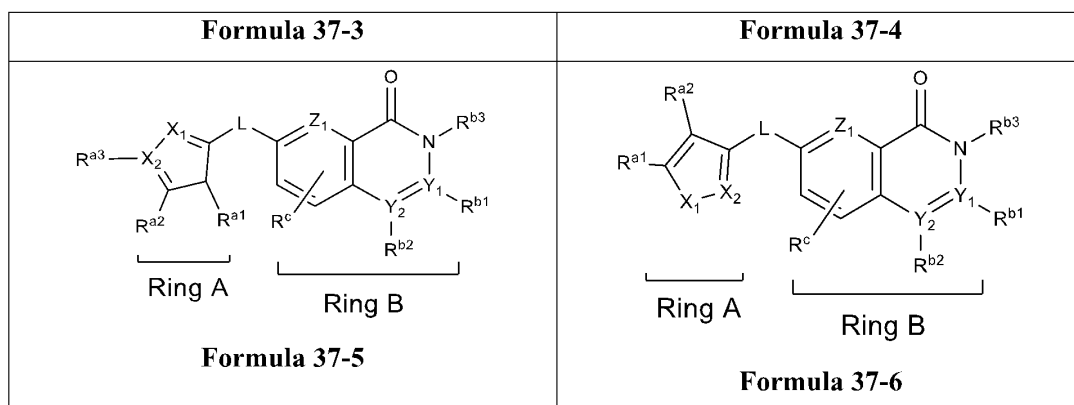
[00156] In a 33rd embodiment, a compound of the disclosure is a compound of the following structural Formula 36-1, 36-2, or and 36-3:



a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X_1 and X_2 are independently selected from N, O, and S, Y_1 , Y_2 , and Z_1 are independently selected from C and N, R^{a1} and R^{a2} are each independently selected from F, Cl, Br, C_1 to C_4 alkyl, CF_3 , CF_2H , CN, $CONH_2$, CH_2NH_2 , and OCH_3 , R^{a3} is C_1 to C_4 alkyl, R^{b1} and R^{b2} are independently selected from H, F, Cl, Br, methyl, CN, CF_3 , CF_2H , ethyl, cyclopropyl, and OCH_3 , wherein R^{b1} and R^{b2} are absent when connected to N in Ring B, and R^c is H, halogen, CN, or methyl; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

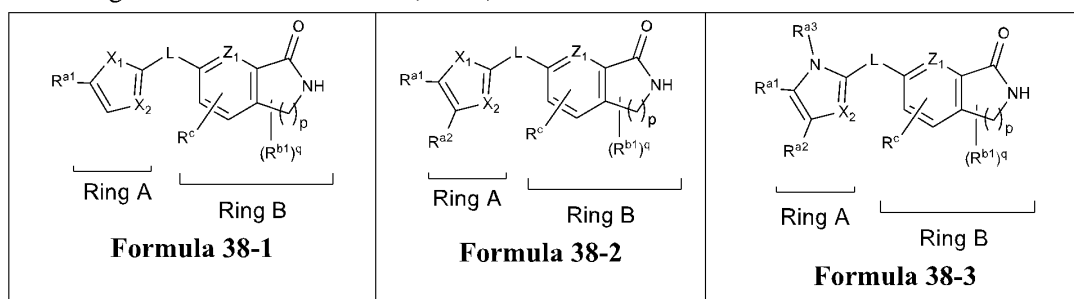
- 10 [00157] In a 34th embodiment, a compound of the disclosure is a compound of the following structural Formula 37-1, 37-2, 37-3, 37-4, 37-5, or 37-6:





a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X_1 and X_2 are independently selected from N, O, and S, Y_1 , Y_2 , and Z_1 are independently selected from C and N, R^{a1} and R^{a2} are each independently selected from F, Cl, Br, C_1 to C_4 alkyl optionally substituted with 1-3 groups of halogen, C_3 - C_4 cycloalkyl, CF_3 , CF_2H , CN, $CONH_2$, CH_2NH_2 , and OCH_3 , R^{a3} is selected from C_3 - C_4 cycloalkyl and C_1 to C_4 alkyl optionally substituted by 1 to 3 groups selected from halogen, cyclopropyl, and 4- to 5-membered heterocyclyl, R^{b1} and R^{b2} are independently selected from H, F, Cl, Br, methyl, CN, CF_3 , CF_2H , ethyl, cyclopropyl, and OCH_3 , wherein R^{b1} and R^{b2} are absent when connected to N in Ring B, R^{b3} is selected from 5-6-membered heteroaryl substituted with 1-2 groups selected from F, Cl, Br, Me, CF_3 , CF_2H , CN, $CONH_2$, and NH_2 , and C_1 to C_4 alkyl optionally substituted with OH or $-C(=O)NH_2$, and R^c is H, halogen, CN, or methyl; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

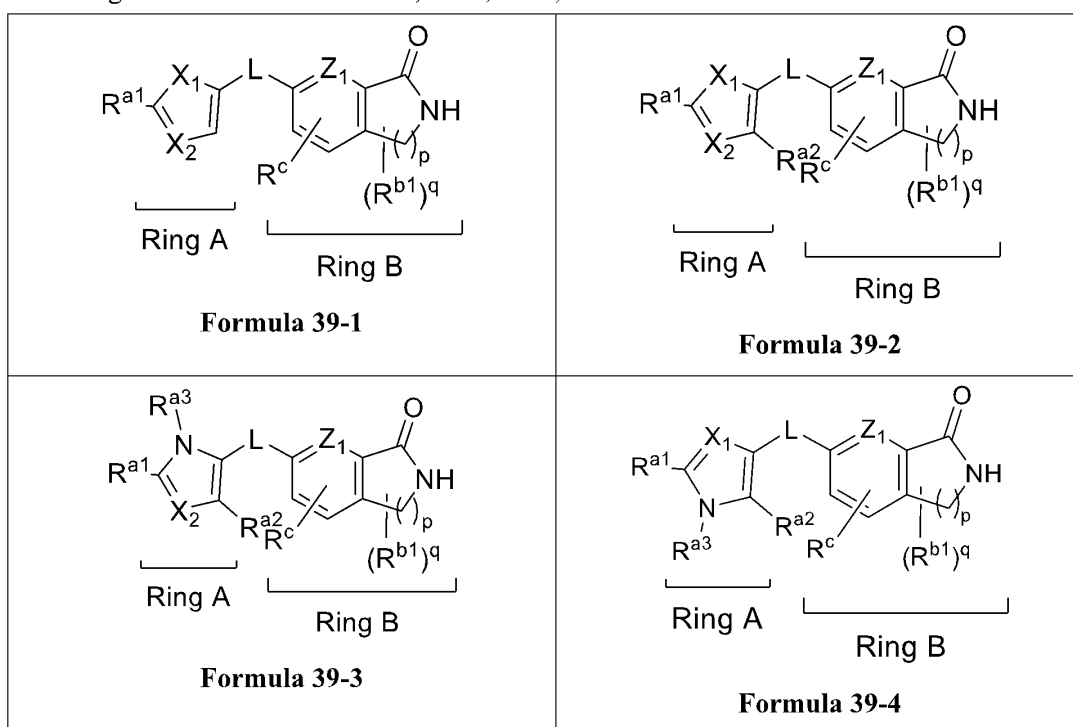
[00158] In a 35th embodiment, a compound of the disclosure is a compound of the following structural Formula 38-1, 38-2, or 38-3:



a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X_1 and X_2 are independently selected from N, O, and S, Z_1 is selected from C and N, R^{a1} and R^{a2} are each independently

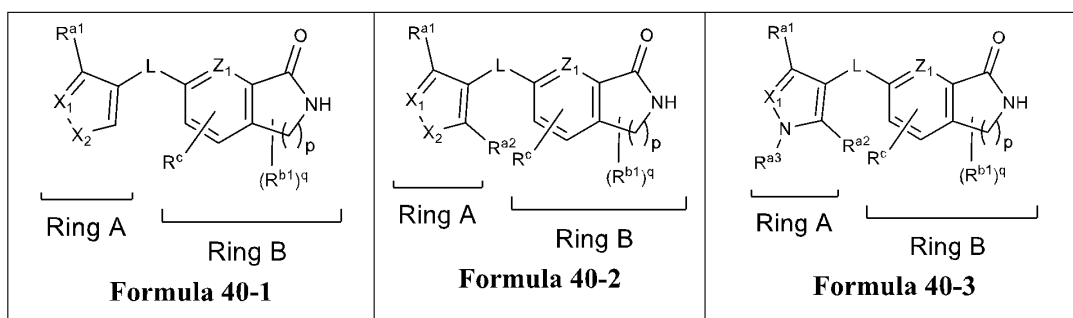
selected from F, Cl, Br, C₁ to C₄ alkyl, CF₃, CF₂H, CN, CONH₂, CH₂NH₂, and OCH₃, R^{a3} is C₁ to C₄ alkyl, R^{b1} is selected from F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, cyclopropyl, and OCH₃, and R^c is H, halogen, CN, or methyl, p is 1, 2, or 3, and q is 0, 1, or 2; and all other variables not specifically defined herein are as defined in any one of the suitable preceding
5 embodiments.

[00159] In a 36th embodiment, a compound of the disclosure is a compound of the following structural Formula 39-1, 39-2, 39-3, or 39-4:



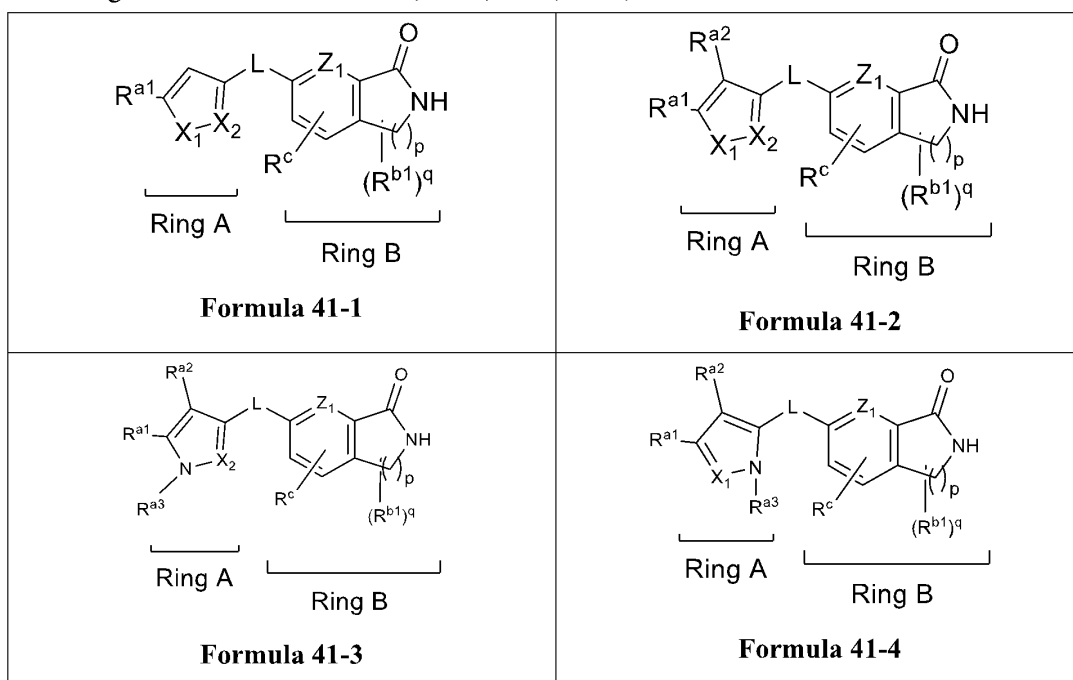
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X₁ and X₂ are independently
10 selected from N, O, and S, Z₁ is selected from C and N, R^{a1} and R^{a2} are each independently selected from F, Cl, Br, C₁ to C₄ alkyl, CF₃, CF₂H, CN, CONH₂, CH₂NH₂, and OCH₃, R^{a3} is C₁ to C₄ alkyl, R^{b1} is selected from F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, cyclopropyl, and OCH₃, R^c is H, halogen, CN, or methyl, p is 1, 2, or 3, and q is 0, 1, or 2; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

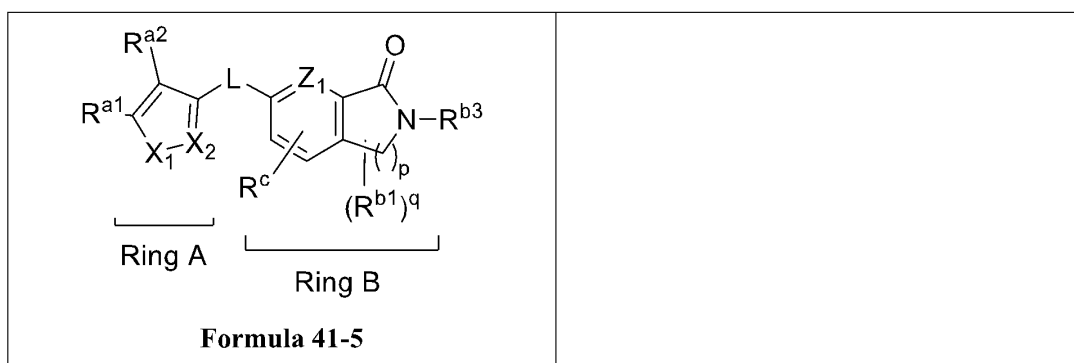
15 [00160] In a 37th embodiment, a compound of the disclosure is a compound of the following structural Formula 40-1, 40-2, or 40-3:



a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X₁ and X₂ are independently selected from N, O, and S, Z₁ is selected from C and N, R^{a1} and R^{a2} are each independently selected from F, Cl, Br, C₁ to C₄ alkyl, CF₃, CF₂H, CN, CONH₂, CH₂NH₂, and OCH₃, R^{a3} is C₁ to C₄ alkyl, R^{b1} is selected from F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, cyclopropyl, and OCH₃, R^c is H, halogen, CN or methyl, p is 1, 2, or 3, and q is 0, 1, or 2; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

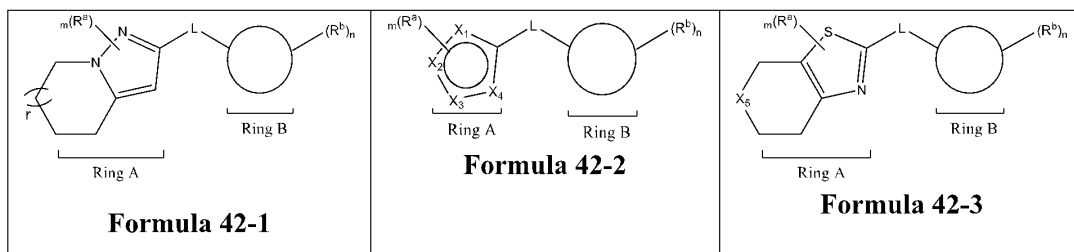
[00161] In a 38th embodiment, a compound of the disclosure is a compound of the following structural Formula 41-1, 41-2, 41-3, 41-4, or 41-5:





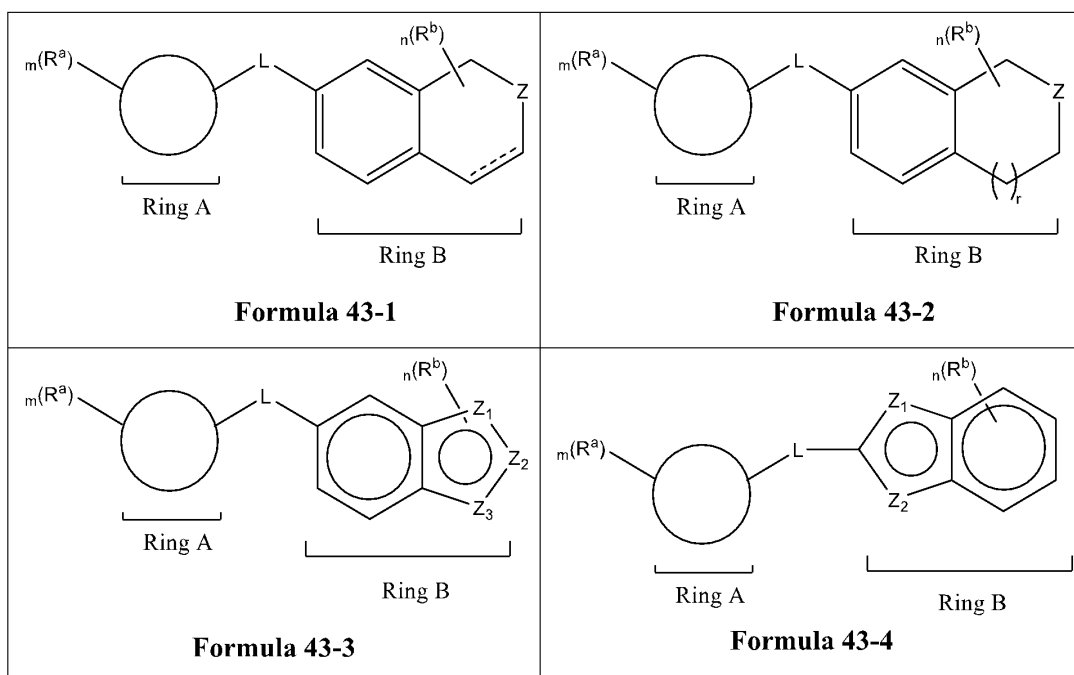
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X_1 and X_2 are independently selected from N, O, and S, Z_1 is selected from C and N, R^{a1} and R^{a2} are each independently selected from F, Cl, Br, C_1 to C_4 alkyl, CF_3 , CF_2H , CN, $CONH_2$, CH_2NH_2 , and OCH_3 , R^{a3} is C_1 to C_4 alkyl, R^{b1} is selected from F, Cl, Br, methyl, CN, CF_3 , CF_2H , ethyl, cyclopropyl, and OCH_3 , R^{b3} is selected from C_1 to C_4 alkyl optionally substituted with OH or $-C(=O)NH_2$, R^c is H, halogen, CN, or methyl, p is 1, 2, or 3, and q is 0, 1, or 2; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00162] In a 39th embodiment, a compound of the disclosure is a compound of the following structural Formula 42-1, 42-2, or 42-3:



a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X_1 , X_2 , X_3 , and X_4 are independently selected from C, N, and S, and wherein X_5 is selected from C and N, and r is an integer selected from 0, 1, and 2; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

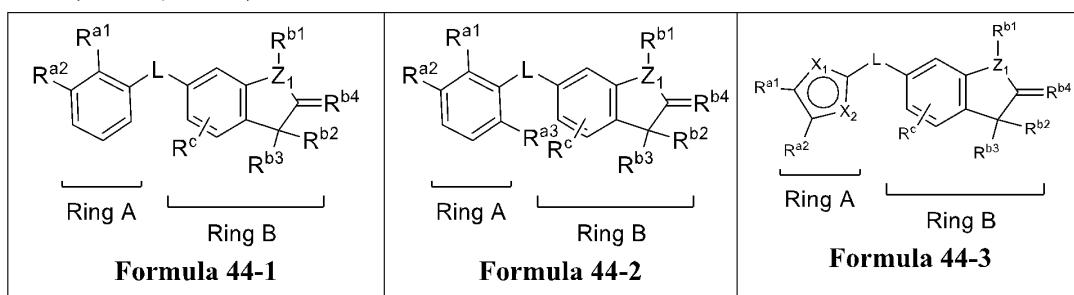
[00163] In a 40th embodiment, a compound of the disclosure is a compound of the following structural Formula 43-1, 43-2, 43-3, or 43-4:

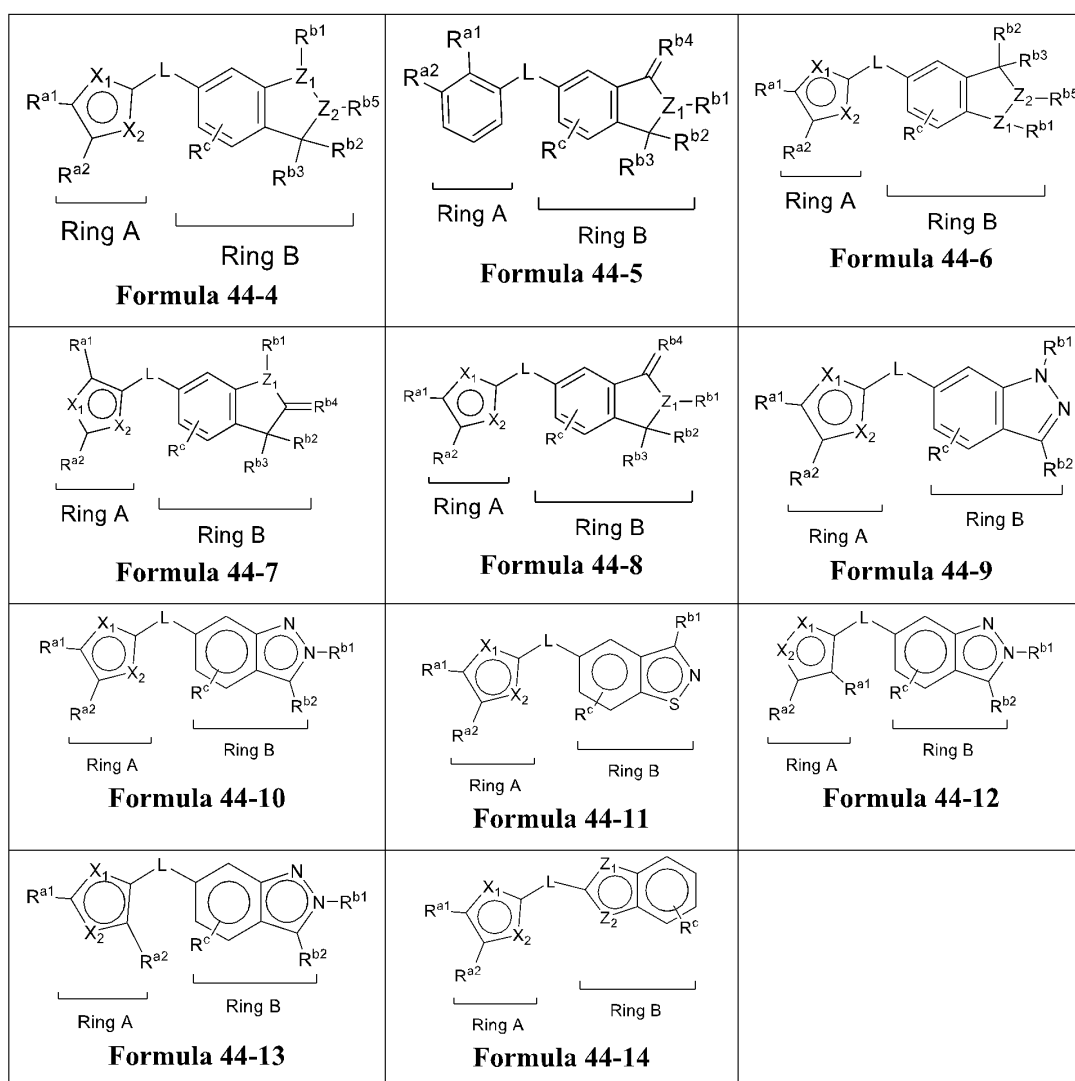


a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein Z, Z₁, Z₂, and Z₃ are independently selected from C, S, and N, and r is an integer selected from 0, 1, and 2; and

5 all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00164] In a 41st embodiment, a compound of the disclosure is a compound of the following structural Formula 44-1, 44-2, 44-3, 44-4, 44-5, 44-6, 44-7, 44-8, 44-9, 44-10, 44-11, 44-12, 44-13, or 44-14:



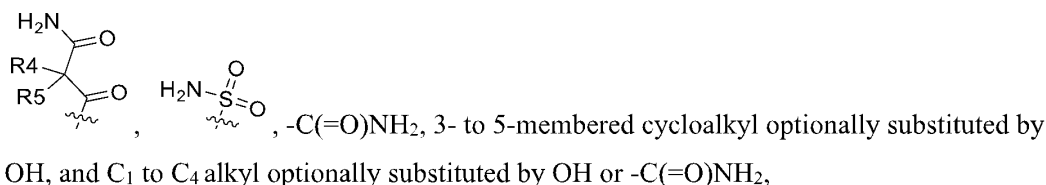


a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein:

X₁ is selected from C, S, O and N, X₂ is selected from C, N, S, and O, Z₁ and Z₂ are independently selected from C, N, and S,

- 5 R^{a1}, R^{a2}, and R^{a3} are each independently selected from F, Cl, Br, C₁ to C₄ alkyl, CF₃, CF₂H, CN, CONH₂, CH₂NH₂, and OCH₃,

R^{b1} is selected from H, F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, OCH₃, -C(=O)CH₂C(=O)NH₂, -C(=O)(C₁ to C₄ alkyl), -C(=O)(C₃ to C₅ cycloalkyl), -C(=O)(5- to 6-membered heteroaryl), -C(=O)(4- to 6-membered heterocyclyl optionally substituted with =O or OH), -C(=O)OH, OH,



R^{b2} and R^{b3} are independently selected from H, F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, -C(=O)NH₂, and OCH₃, or R^{b2} and R^{b3} join to form a C₃ to C₅ cycloalkyl,

5 R^{b4} is =O or absent,

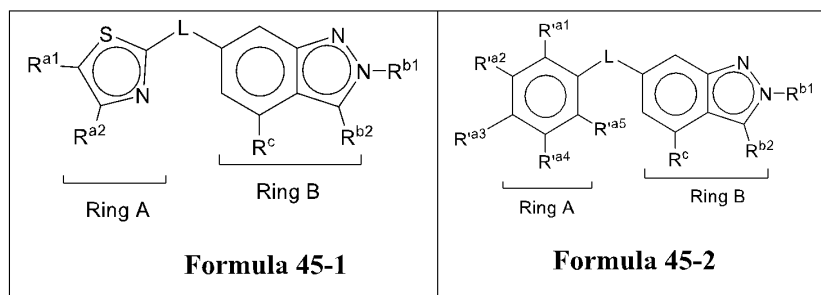
R^{b5} is selected from H, F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, OCH₃, -C(=O)CH₂C(=O)NH₂, -C(=O)(C₁ to C₄ alkyl), -C(=O)(C₃ to C₅ cycloalkyl), -C(=O)(5- to 6-membered heteroaryl), -C(=O)(5- to 6-membered heterocyclyl optionally substituted with =O), -C(=O)OH, OH, C₁ to C₄ alkyl optionally substituted by OH or -C(=O)NH₂, and C₃ to C₅ cycloalkyl optionally

10 substituted with OH, and

R^c is H, halogen, CN, or methyl, and

wherein R₄ and R₅ join to form a 3 to 4-membered cycloalkyl; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00165] In a 42nd embodiment, a compound of the disclosure is a compound of the
15 following structural Formula 45-1 or 45-2:



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

R^{a1} and R^{a2} are each independently selected from halogen and C₁ to C₂ alkyl optionally substituted with 1 to 3 groups of halogen,

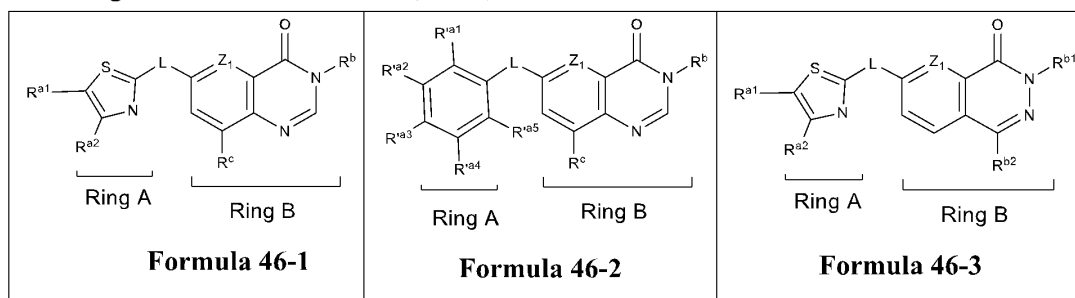
20 R^{a1}, R^{a2}, R^{a3}, R^{a4}, and R^{a5} are each independently selected from H and halogen, wherein 2, 3, or 4 of R^{a1}, R^{a2}, R^{a3}, R^{a4}, and R^{a5} are halogen and the rest is H,

R^{b1} is selected from H and C₁ to C₄ alkyl optionally substituted by -C(=O)NH₂,

R^{b2} is selected from H and C_1 to C_4 alkyl optionally substituted by 1-3 groups of halogen, and

R^c is selected from H, halogen, and C_1 to C_2 alkyl; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00166] In a 43rd embodiment, a compound of the disclosure is a compound of the following structural Formula 46-1, 46-2, or 46-3:



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

Z_1 is selected from C and N,

R^{a1} and R^{a2} are each independently selected from halogen and C_1 to C_2 alkyl optionally substituted with 1 to 3 groups of halogen,

R^{a1} , R^{a2} , R^{a3} , R^{a4} , and R^{a5} are each independently selected from H and halogen, wherein 2, 3, or 4 of R^{a1} , R^{a2} , R^{a3} , R^{a4} , and R^{a5} are halogen and the rest is H,

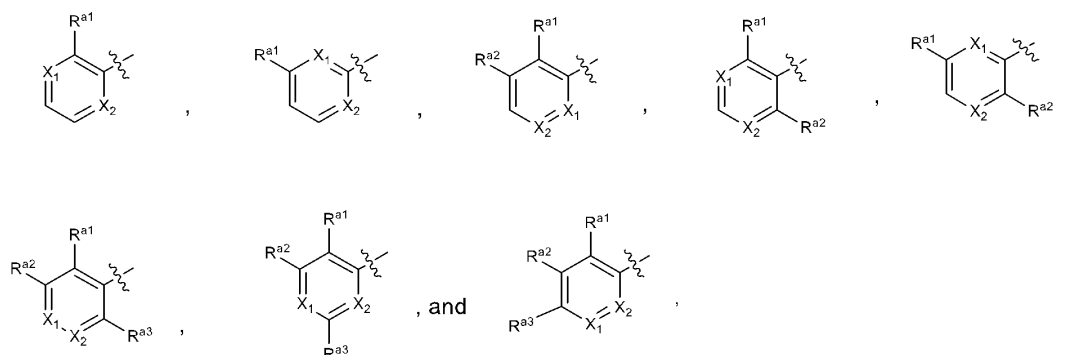
R^b is selected from H and 5- to 6-membered heteroaryl containing 2 to 3 heteroatoms selected from N and S, wherein the 5- to 6-membered heteroaryl of R^b is optionally substituted by 1 to 3 groups selected from halogen and C_1 to C_4 alkyl,

R^{b1} is selected from H and C_1 to C_4 alkyl optionally substituted by $-C(=O)NH_2$,

R^{b2} is selected from H, halogen, $-O(C_1$ to C_4 alkyl), and C_1 to C_4 alkyl optionally substituted with 1-3 groups of halogen, and

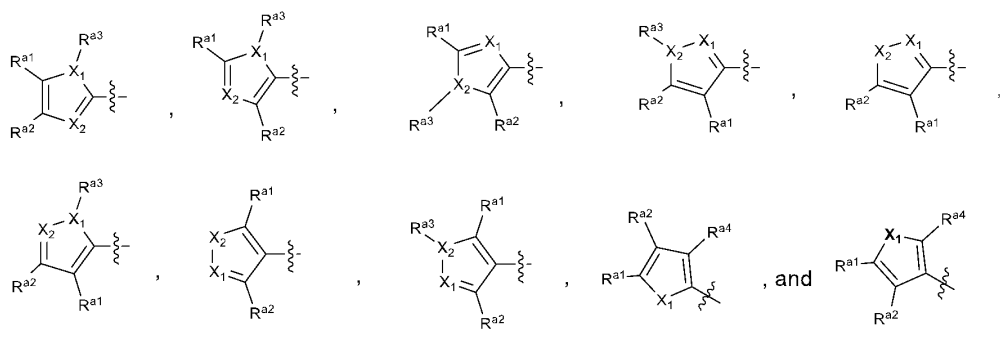
R^c is selected from H, halogen, and C_1 to C_2 alkyl; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00167] In a 44th embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, Ring A substituted with m groups of R^a is selected from:



wherein R^{a1} , R^{a2} , and R^{a3} are independently selected from F, Cl, Br, methyl, CF_3 , CF_2H , and cyclopropyl, and X_1 and X_2 are independently selected from C and N; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

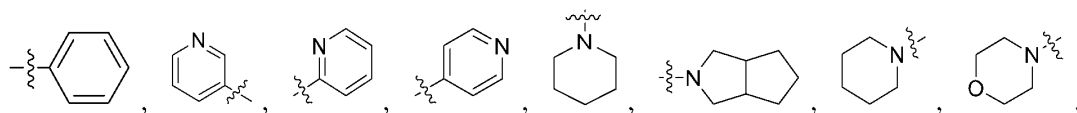
- 5 [00168] In a 45th embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, Ring A substituted with m groups of R^a is selected from:

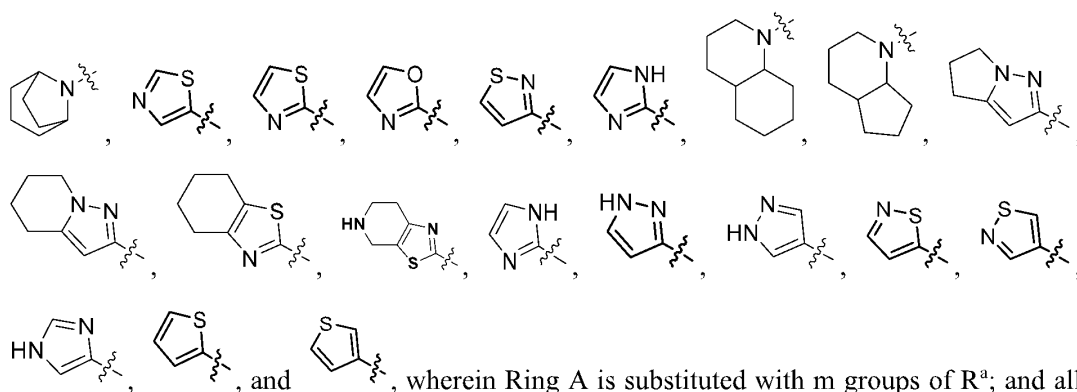


wherein R^{a1} and R^{a2} are independently selected from H, CN, F, Cl, Br, C_1 to C_4 alkyl, CF_3 ,

- 10 CF_2H , and OCH_3 , R^{a3} is H, or C_1 to C_4 alkyl, R^{a4} is selected from H, F, Cl, Br, and C_1 to C_4 alkyl, and X_1 and X_2 are independently selected from N, O, and S; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

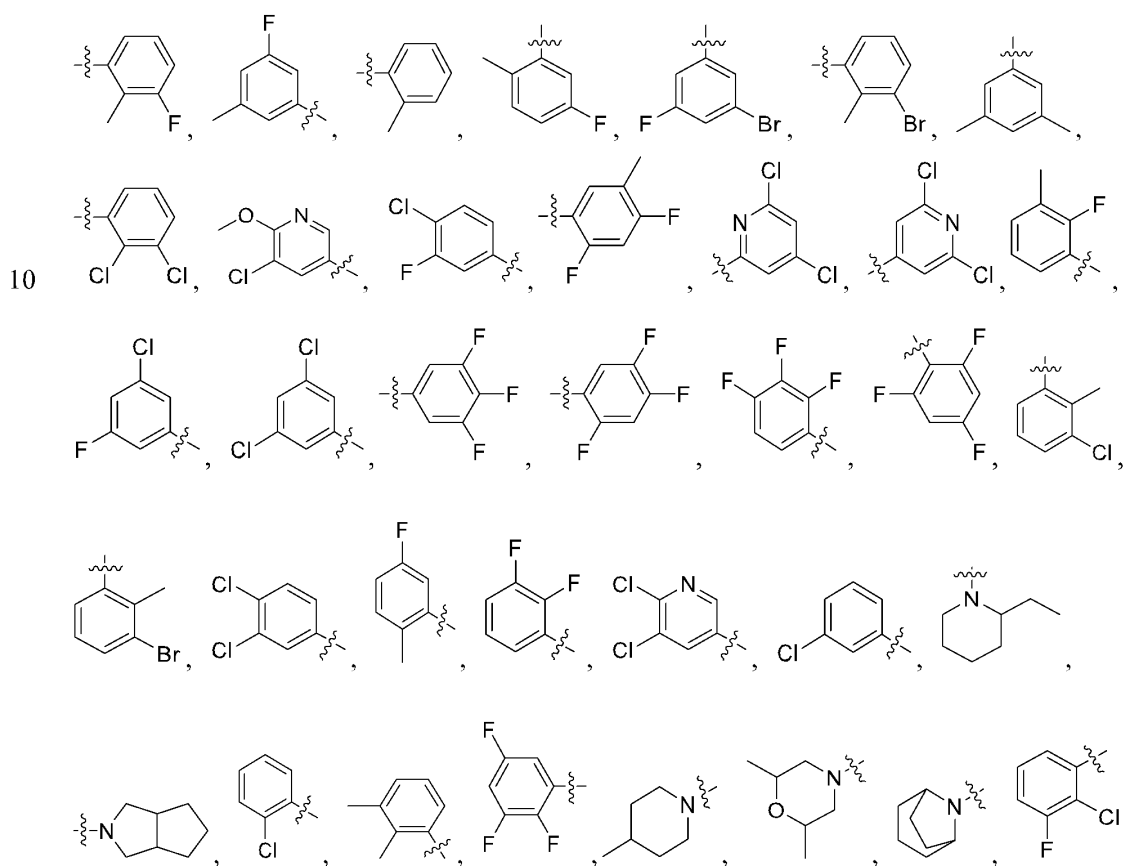
- [00169] In a 46th embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure,
- 15 Ring A is selected from:



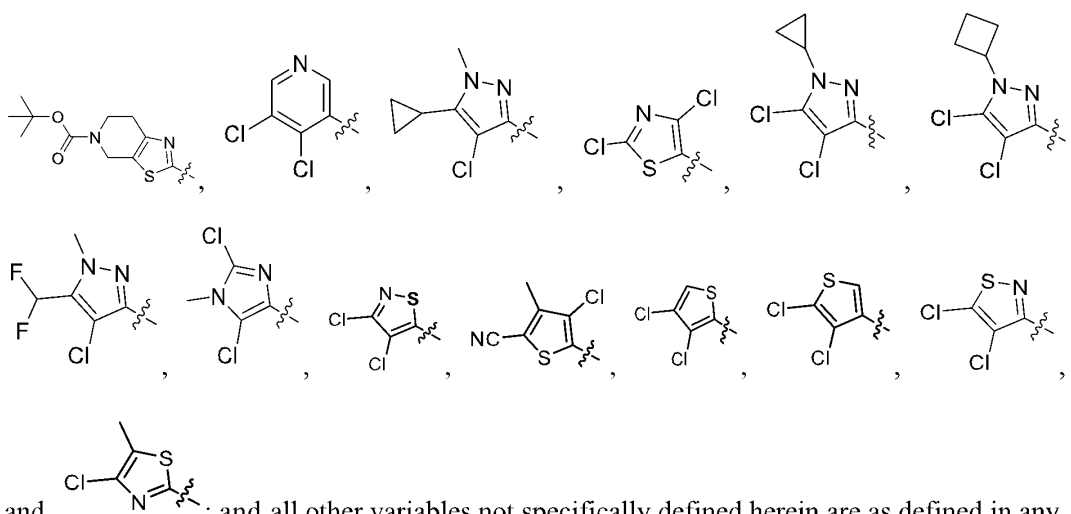


wherein Ring A is substituted with m groups of R^a ; and all other variables not specifically defined herein are as defined in any one of the suitable preceding
 5 embodiments.

[00170] In a 47th embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, Ring A substituted with m groups of R^a is selected from:

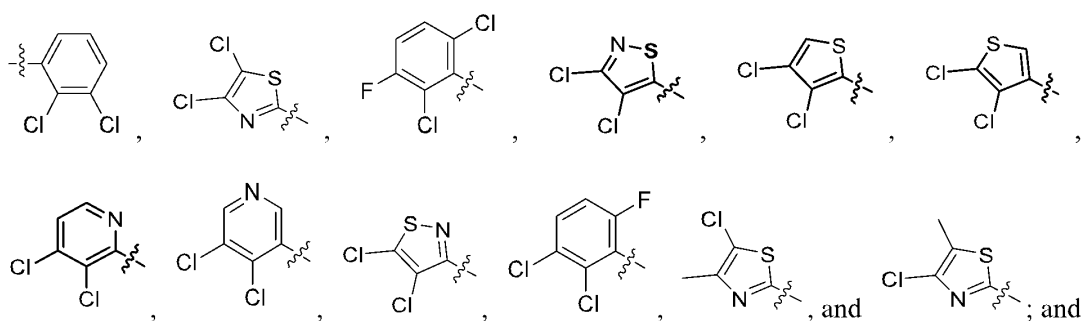






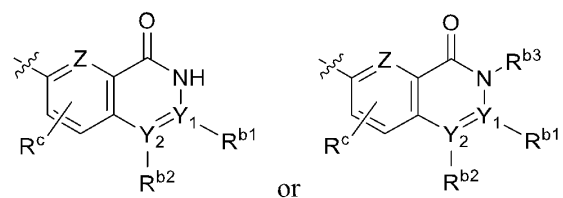
; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

- 5 [00171] In a 48th embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, Ring A substituted with m groups of R^a is selected from:



- 10 all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

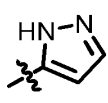
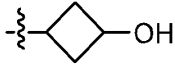
[00172] In a 49th embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure,



Ring B substituted with n groups of R^b is:

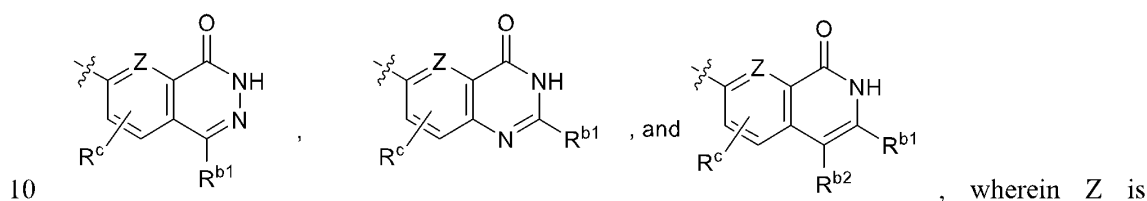
- 15 wherein Z is selected from C and N, Y₁ and Y₂ are independently selected from C and N, R^{b1} and R^{b2} are independently selected from H, F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, cyclopropyl,

and OCH₃, wherein R^{b1} and R^{b2} are absent when connected to N in Ring B, and R^{b3} is selected

from H, methyl, ethyl, , , and 5-membered heteroaryl, wherein the

5-membered heteroaryl of R^{b3} contains 2 to 3 heteroatoms selected from N and S and the 5-membered heteroaryl is optionally substituted with 1-2 groups selected from halogen and C₁ to C₄ alkyl, and R^c is selected from H, halogen, CN, and methyl; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

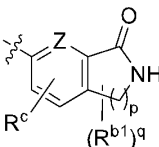
[00173] In a 50th embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, Ring B substituted with n groups of R^b is selected from:



selected from C and N, R^{b1} is selected from H, F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, cyclopropyl, and OCH₃, R^{b2} is selected from H, F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, cyclopropyl, and OCH₃, and R^c is selected from H, halogen, CN, and methyl; and all other variables not specifically defined herein are as defined in any one of the suitable preceding

15 embodiments.

[00174] In a 51st embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure,

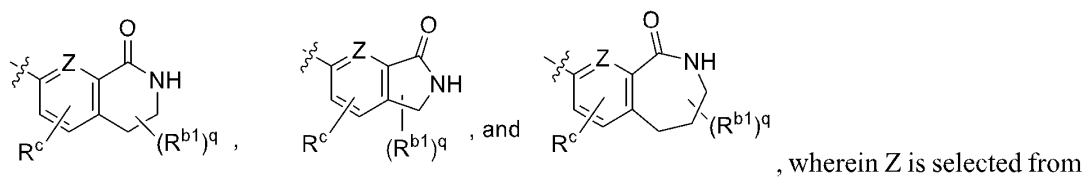
Ring B substituted with n groups of R^b is: , wherein Z is selected from C and N,

R^{b1} is selected from F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, cyclopropyl, and OCH₃, R^c is selected from H, halogen, CN, and methyl, p is 1, 2, or 3, and q is 0, 1, or 2; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

20

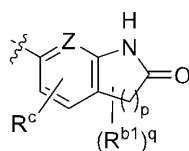
[00175] In a 52nd embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure,

Ring B substituted with n groups of R^b is selected from:



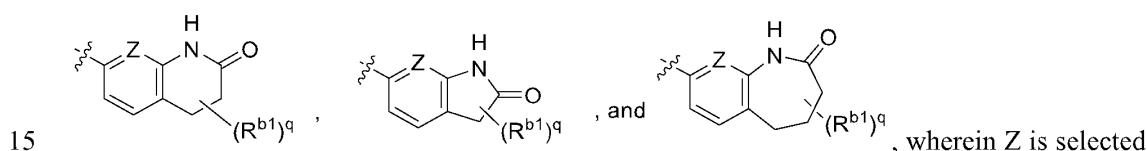
5 specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00176] In a 53rd embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure,



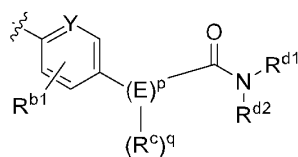
Ring B substituted with n groups of R^b is: , wherein Z is selected from C and N, R^{b1} selected from F, Cl, Br, methyl, CN, CF_3 , CF_2H , ethyl, cyclopropyl, and OCH_3 , R^c is H, halogen, CN, or methyl, p is 1, 2 or 3, q is 0, 1, or 2; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00177] In a 54th embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, Ring B substituted with n groups of R^b is selected from:



from C and N, R^{b1} selected from F, Cl, Br, methyl, CN, CF_3 , CF_2H , ethyl, cyclopropyl, and OCH_3 , and q is 1 or 2; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

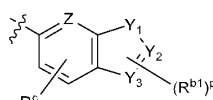
[00178] In a 55th embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure,



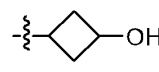
Ring B substituted with n groups of R^b is , wherein Y is selected from

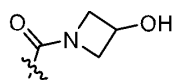
C and N, E is selected from C, N, and O, R^{d1} and R^{d2} are independently selected from H, methyl, ethyl, and cyclopropyl, R^c is selected from F, Cl, Br, methyl, CN, CF_3 , CF_2H , ethyl, cyclopropyl, and OCH_3 , R^{b1} is selected from H, halogen, CN, and methyl, p is 1 or 2, and q is 0, 1, or 2; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00179] In a 56th embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure,



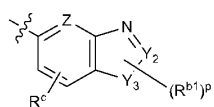
Ring B substituted with n groups of R^b is , wherein Z is selected from C and N, Y_1 , Y_2 , and Y_3 are independently selected from C, N, S, and O, R^{b1} is selected from F, Cl, Br,

10 methyl, CN, CF_3 , CF_2H , ethyl, cyclopropyl, $CONH_2$, OCH_3 , CH_2CONH_2 , , and

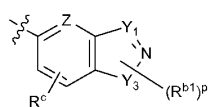


, R^c is selected from H, halogen, CN, and methyl, and p is 0, 1, or 2; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00180] In a 57th embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, Ring B substituted with n groups of R^b is selected from

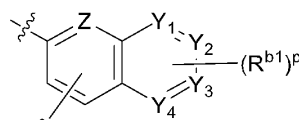


and



; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00181] In a 58th embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure,

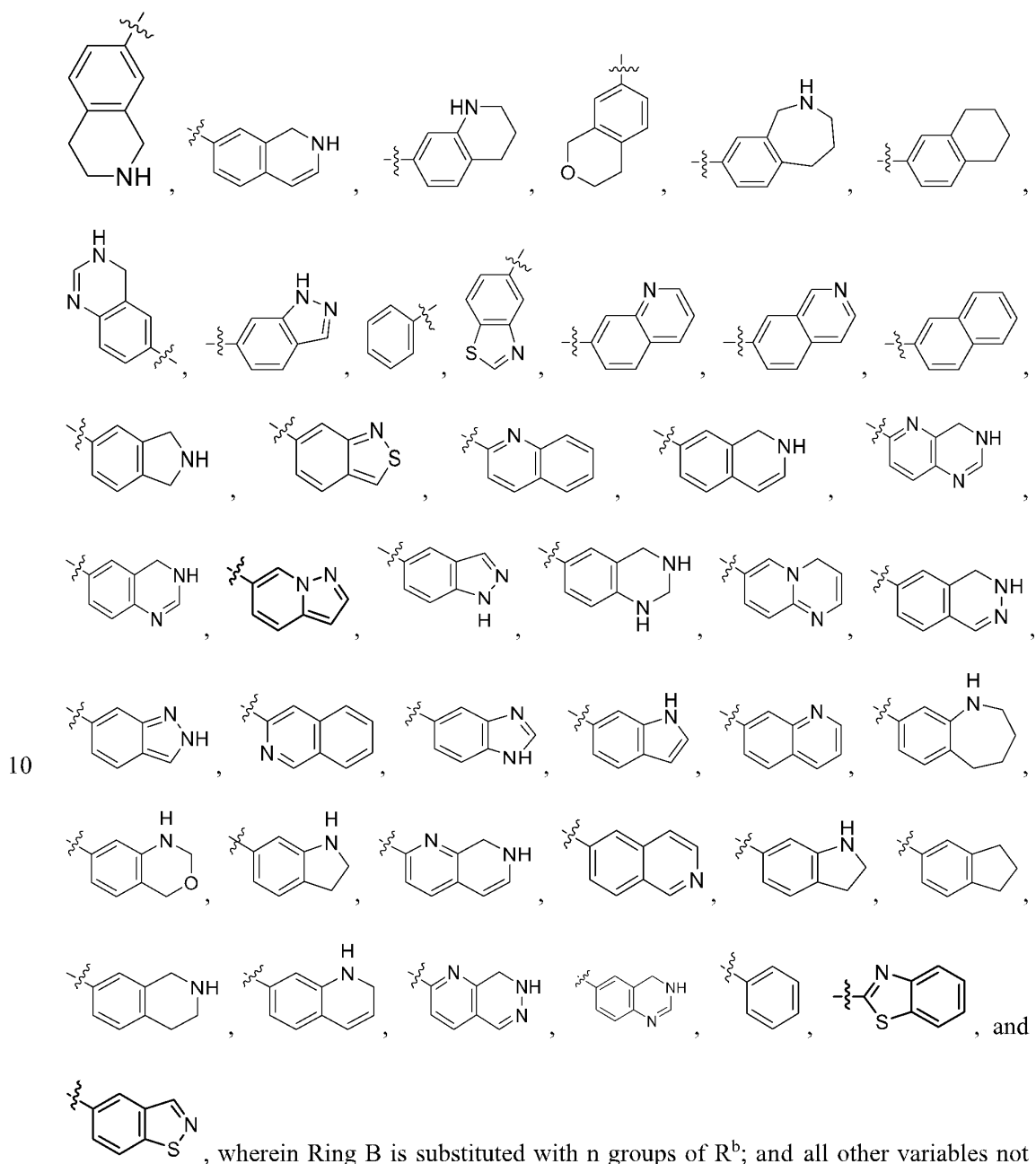


Ring B substituted with n groups of R^b is , Z is selected from C and N, Y_1 , Y_2 , Y_3 , and Y_4 are independently selected from C and N, R^{b1} is selected from F, Cl, Br, methyl, CN, CF_3 , CF_2H , ethyl, cyclopropyl, $CONH_2$, and OCH_3 , R^c is H, halogen, CN, or methyl,

and p is 0, 1, or 2; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

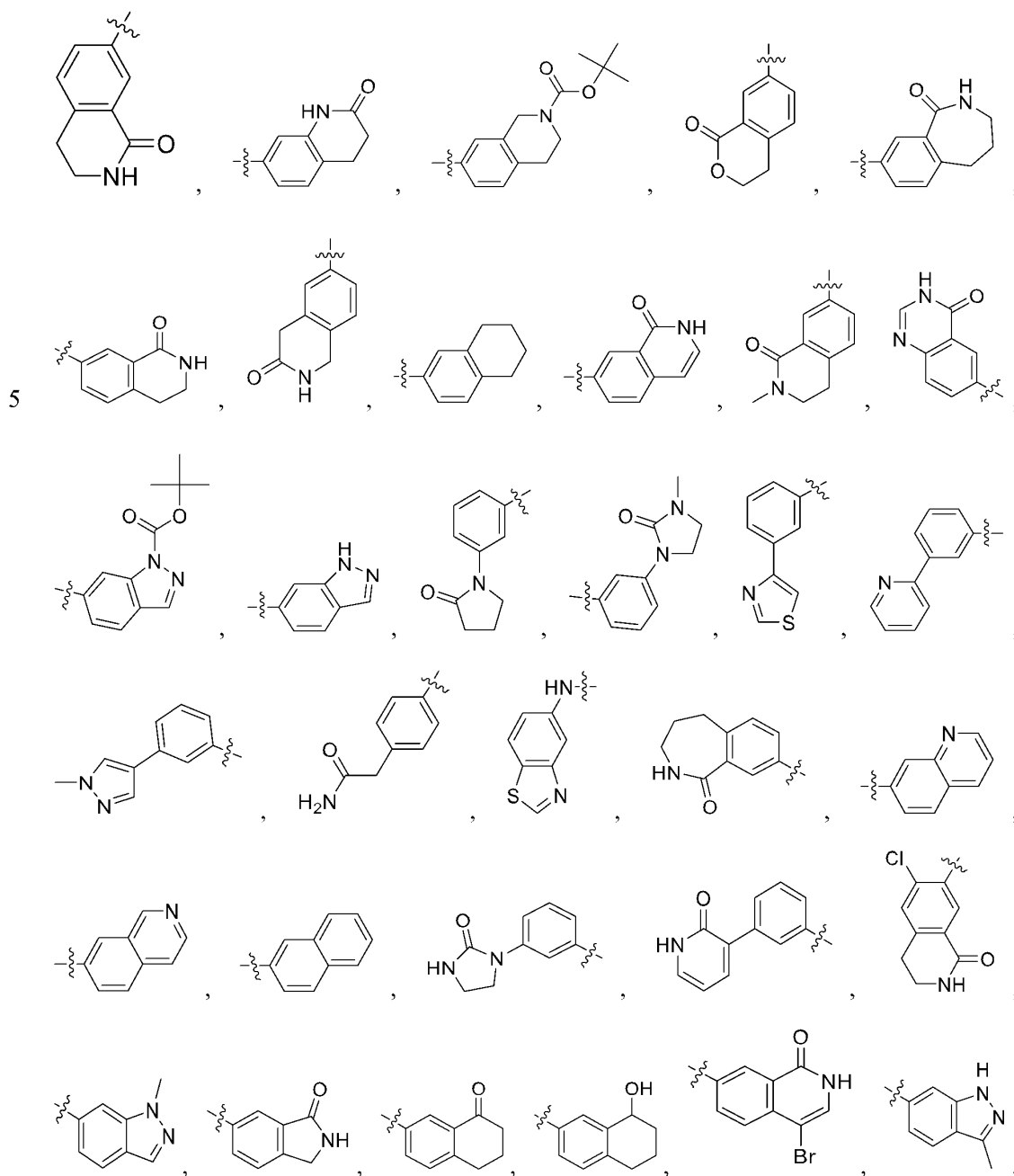
[00182] In a 59th embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure,

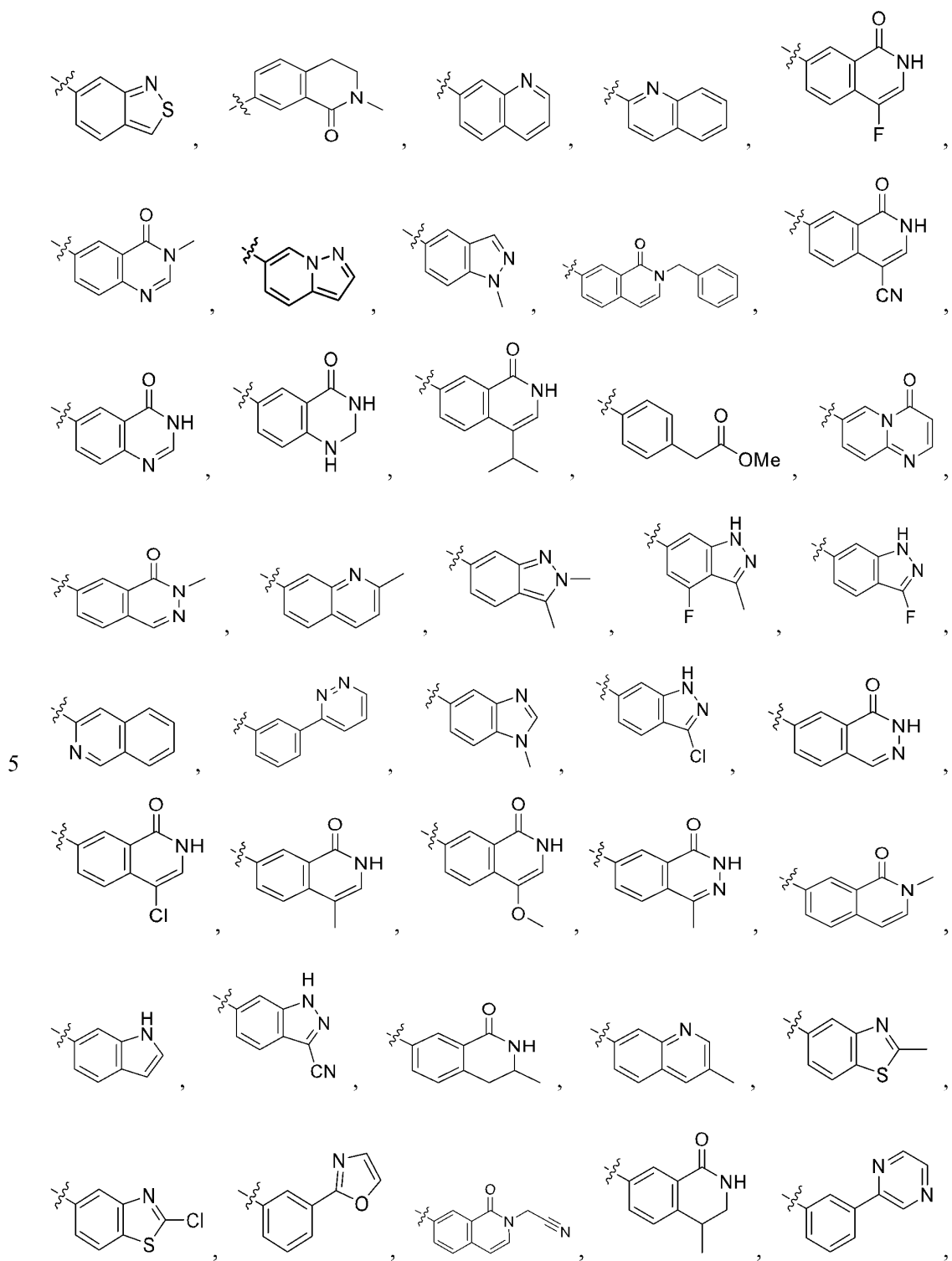
5 Ring B is selected from:



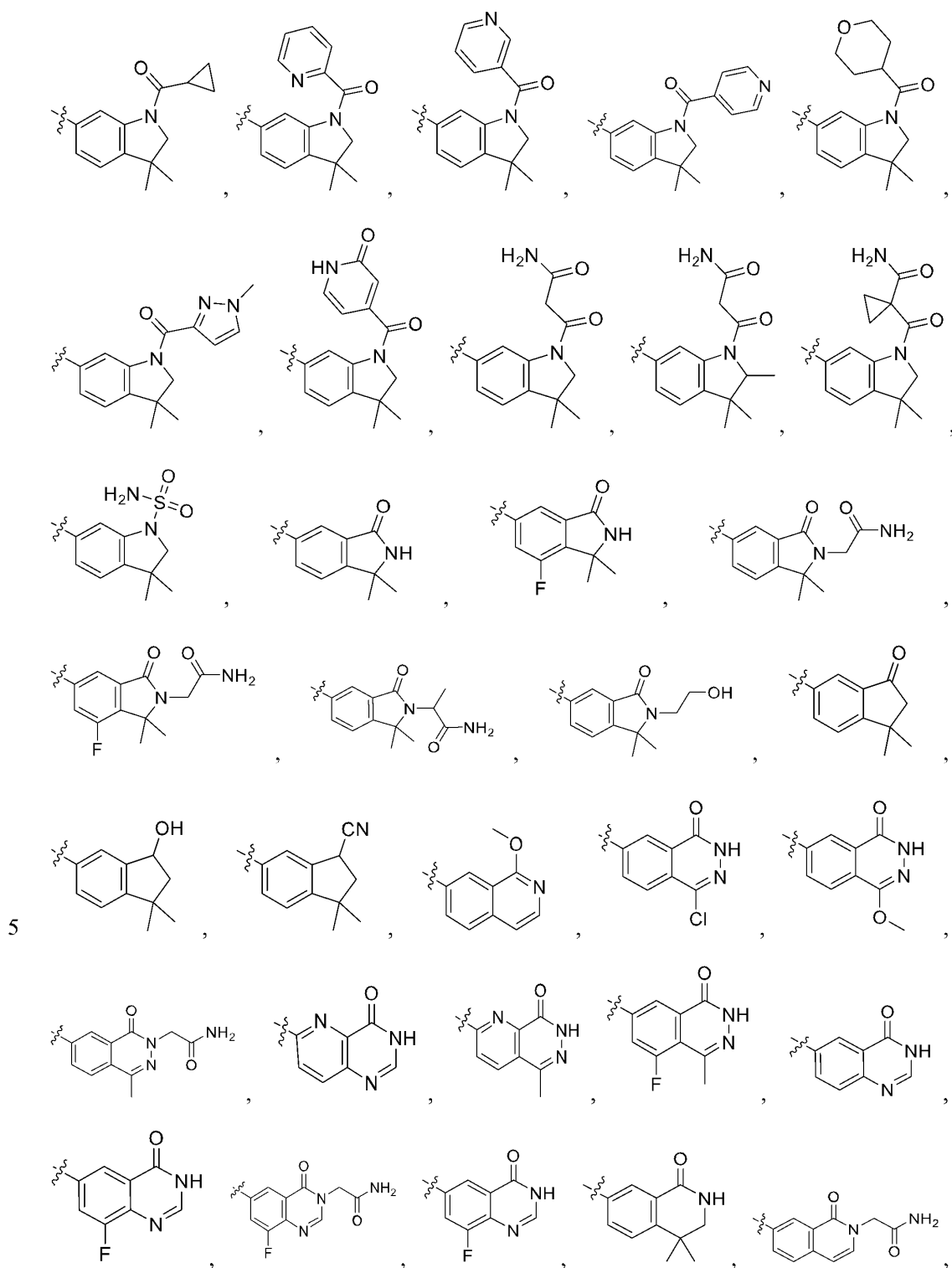
specifically defined herein are as defined in any one of the suitable preceding embodiments.

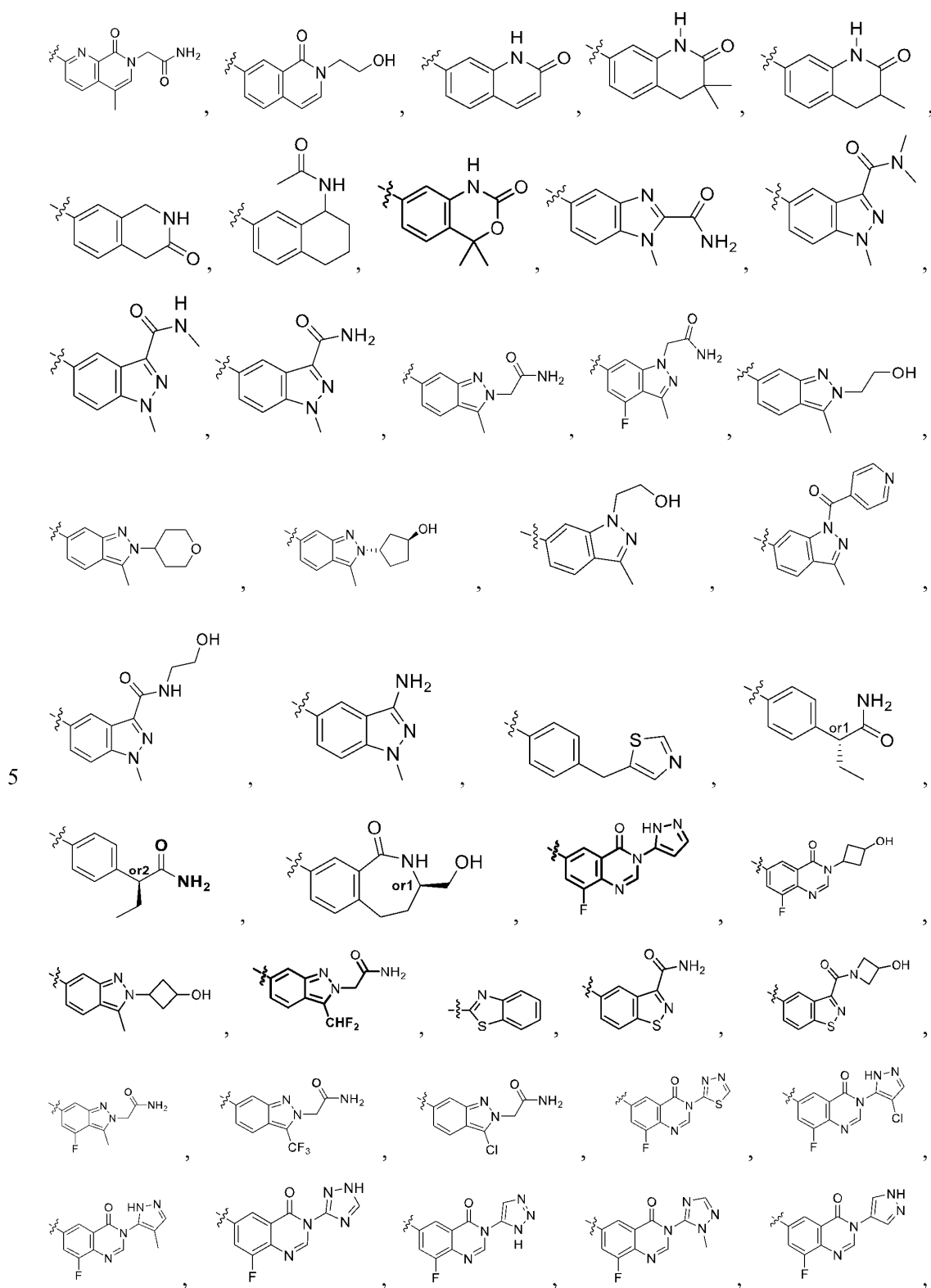
[00183] In a 60th embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, Ring B substituted with n groups of R^b is selected from:

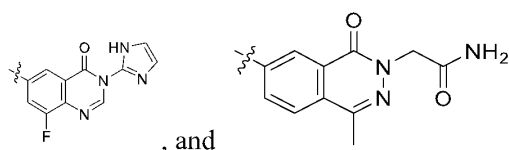






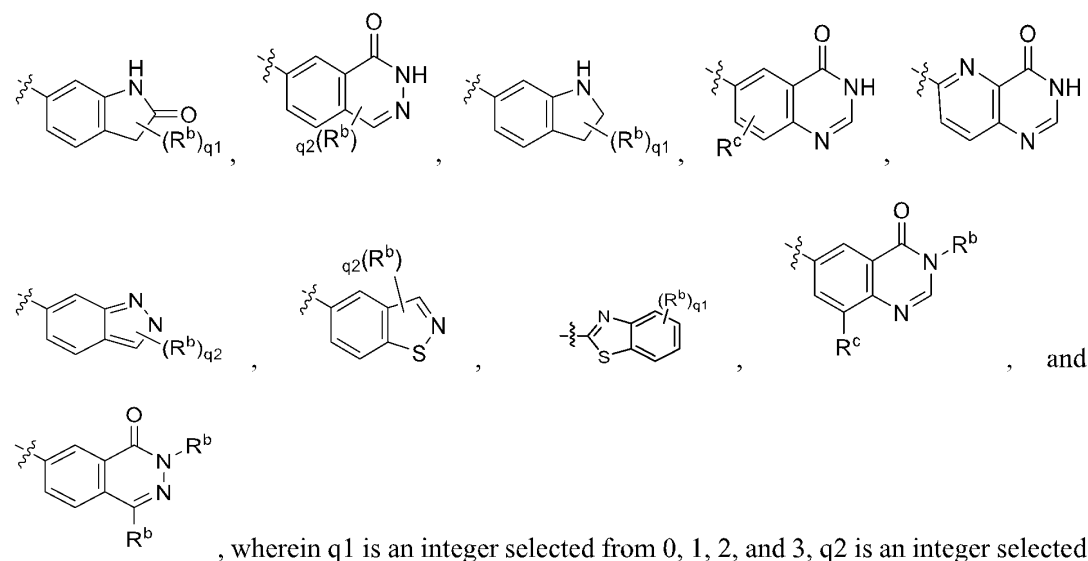
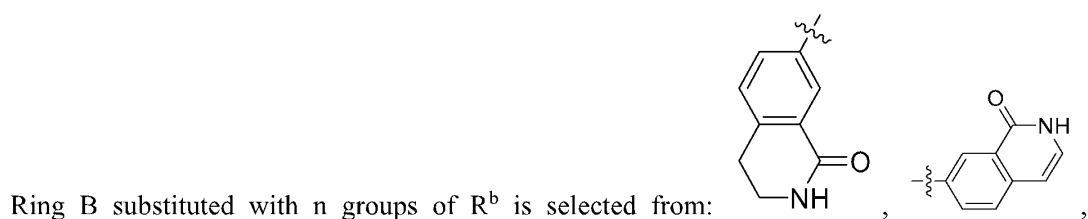






and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00184] In a 61st embodiment, in a compound, tautomer, a solvate or stereoisomer
5 of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure,



10 from 0, 1, and 2, and R^c is selected from F, Cl, Br and Me; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00185] In a 62nd embodiment, in a compound, tautomer, a solvate or stereoisomer
of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure,
wherein R^a is selected from C₃-C₅ cycloalkyl, -O(C₁-C₂ alkyl), COOH, CN, CONH₂, -
15 C(=O)NH(C₁-C₂ alkyl), -C(=O)N(C₁-C₂ alkyl)₂, -C(=O)O(C₁-C₂ alkyl), halogen, and C₁-C₂
alkyl optionally substituted with 1 to 3 groups selected from halogen; and all other variables

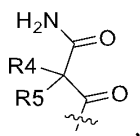
not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00186] In a 63rd embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, R^a is selected from CH₃, CH₂CH₃, CH₂CF₃, F, Cl, Br, C₃-C₄ cycloalkyl, COOH, CN, CONH₂, -
 5 C(=O)NHCH₃, -C(=O)N(CH₃)₂, -NC(=O)N(CH₃)₃, and OCH₃; and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

[00187] In a 64th embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, R^b is selected from =O, OH, halogen, CN, -C(=O)NH(C₁-C₄ alkyl), -C(=O)O(C₁-C₄ alkyl), -
 10 C(=O)NH₂,

C₃-C₄ cycloalkyl optionally substituted with OH,

O(C₁-C₃ alkyl), -C(=O)(C₁-C₂ alkyl), -C(=O)(C₃-C₆ cycloalkyl), -C(=O)(4- to 6-
 membered heterocyclyl optionally substituted with =O), -C(=O)(5- to 6-membered
 heteroaryl optionally substituted with C₁-C₂ alkyl or NH₂), -C(=O)(CH₂)_pC(=O)NH₂, -
 15 NHC(=O)(C₁-C₂ alkyl), -C(=O)N(C₁-C₂ alkyl)₂, -C(=O)NH(CH₂)_pOH, -S(=O)₂NH₂,



C₁-C₃ alkyl optionally substituted with 1 to 3 groups selected from halogen, NH₂, OH,
 OCH₃, -C(=O)NH(C₁-C₄ alkyl), -C(=O)O(C₁-C₄ alkyl), -C(=O)N(C₁-C₄ alkyl)₂, -COOH, -
 C(=O)NH₂, CN, C₃-C₄ cycloalkyl, phenyl, -C(=O)(C₁-C₂ alkyl), -C(=O)(C₃-C₆ cycloalkyl),
 20 -C(=O)(5- to 6-membered heterocyclyl), -C(=O)(5- to 6-membered heteroaryl optionally
 substituted with C₁-C₂ alkyl), C(=O)NH(CH₂)_pOH, and 5- to 6-membered heteroaryl,

5- to 6- membered heteroaryl optionally substituted with 1 to 2 groups selected from C₁-C₂
 alkyl, and

5- to 6-membered heterocyclyl optionally substituted with 1 to 2 groups selected from =O
 25 and C₁-C₂ alkyl, or

two R^b attached to the same position on Ring B join to form a C₃-C₅ cycloalkyl,

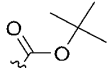
wherein p is an integer selected from 1 and 2, and

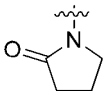
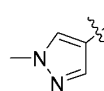
wherein R₄ and R₅ are each independently selected from H and C₁ to C₃ alkyl or R₄ and R₅

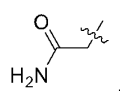
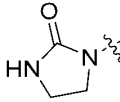
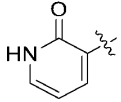
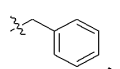
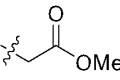
join to form a 3 to 5-membered cycloalkyl;

and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

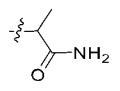
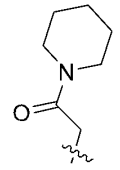
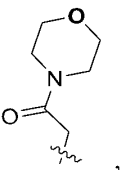
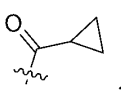
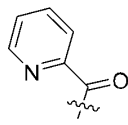
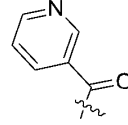
[00188] In a 65th embodiment, in a compound, tautomer, a solvate or stereoisomer
5 of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, R^b

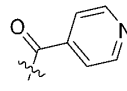
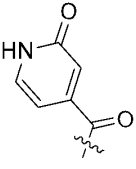
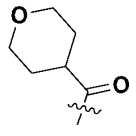
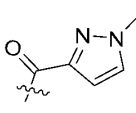
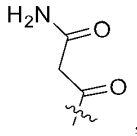
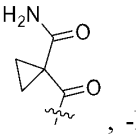
is selected from =O, , CH₃, CHF₂, CF₃, OH, F, Cl, Br, CN, CH(CH₃)₂, CH₂CN, OCH₃,

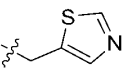
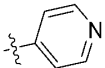
-C(=O)NH₂, -C(=O)OCH₃, , , , , , ,

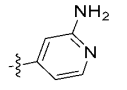
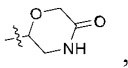
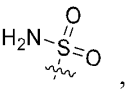
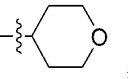
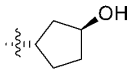
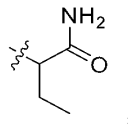
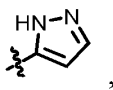
, , , , , CH₂CH₂OH, CH₂CH₂CH₂OH,

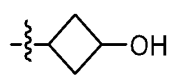
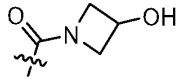
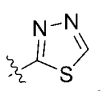
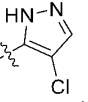
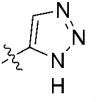
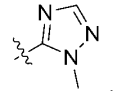
CH₂C(=O)OH, CH₂C(=O)NH₂, CH₂C(=O)NHCH₂CH₂OH, CH₂CH₂CH₂C(=O)NH₂,

10 , , , -C(=O)CH₃, , , ,

, , , , , , -NHC(=O)CH₃,

-C(=O)N(CH₃)₂, -C(=O)NCH₃, NH₂, -C(=O)NHCH₂CH₂OH, , CH₂OH, ,

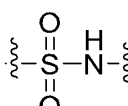
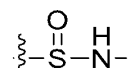
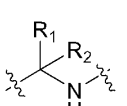
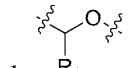
, , , , , , ,

, , , , , , , ,

15 , and , or two R^b attached to the same position on Ring B join to form a 3-membered or 5-membered cycloalkyl; and all other variables not specifically defined herein are

as defined in any one of the suitable preceding embodiments.

[00189] In a 66th embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, L

is selected from , , , and , wherein

- 5 R₁ is H, D, or C₁-C₄ alkyl, and R₂ is selected from CN, C₁-C₄ alkenyl (e.g., C₂, C₃, or C₄ alkenyl), C₃-C₅ cycloalkyl, 5 to 6-membered heteroaryl,

phenyl optionally substituted with 1 to 2 groups selected from C₁-C₃ alkyl (e.g., C₁, C₂, or C₃ alkyl) and halogen, and

- C₁-C₄ alkyl (e.g., C₁, C₂, C₃ or C₄ alkyl) optionally substituted with 1 to 3 groups
10 selected from halo, OH, and phenyl,

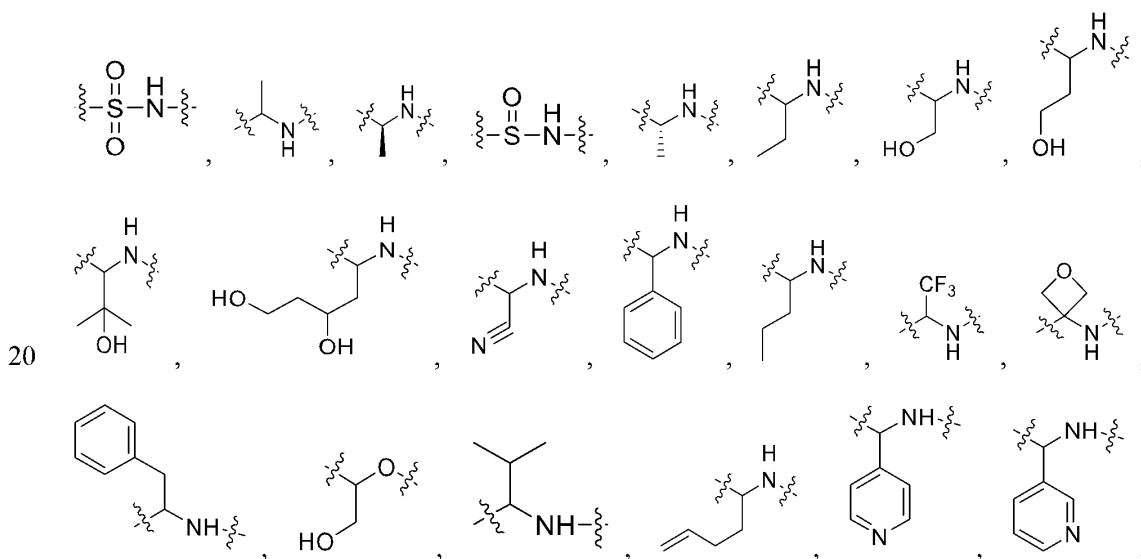
or

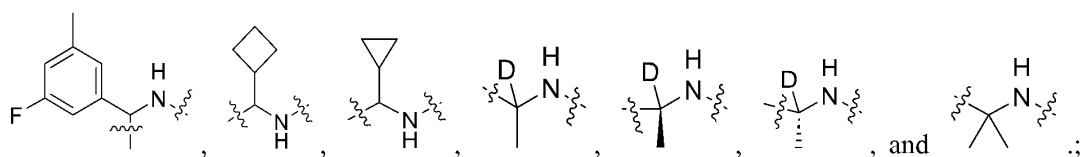
R₁ and R₂ join to form a 3-4 membered heterocyclyl; and

R₃ is C₁-C₄ alkyl (e.g., C₁, C₂, C₃ or C₄ alkyl) optionally substituted with 1 to 3 groups selected from halogen and OH; and all other variables not specifically defined herein are as defined in

- 15 any one of the suitable preceding embodiments.

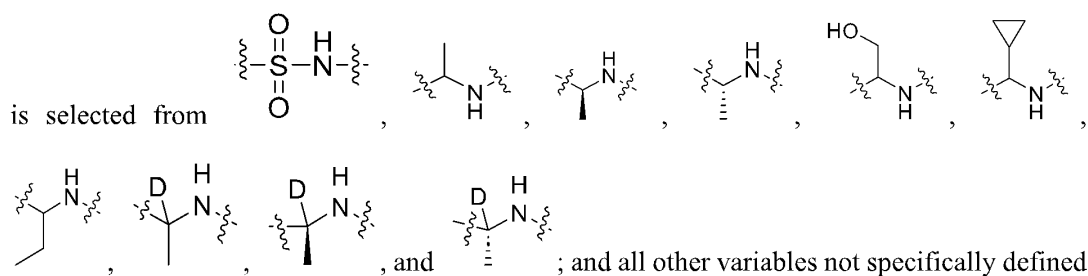
[00190] In a 67th embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, L is selected from:

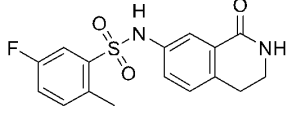
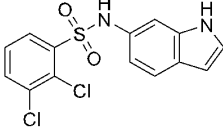
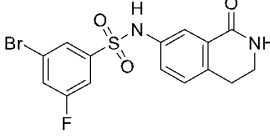
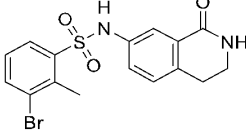
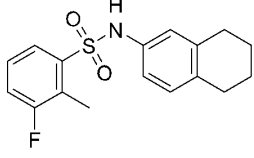
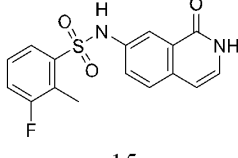
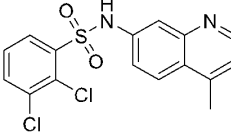
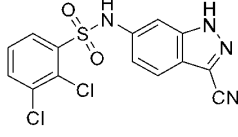
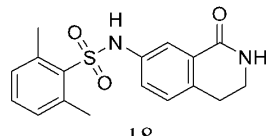
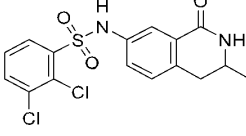
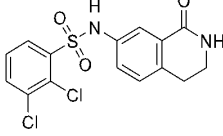
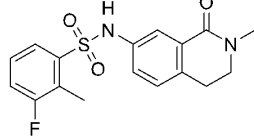
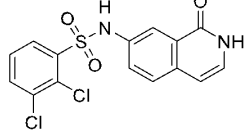
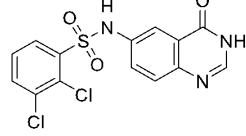
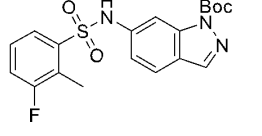
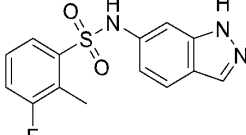
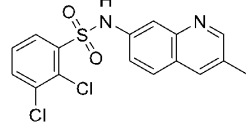
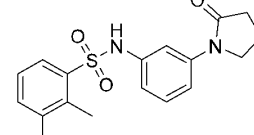
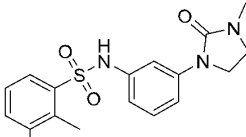
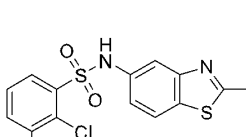
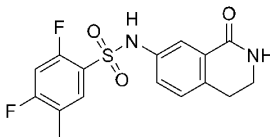
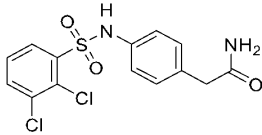
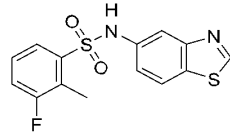
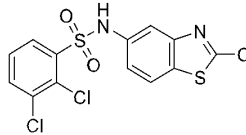


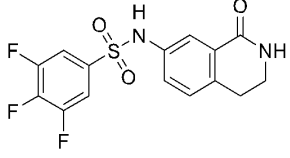
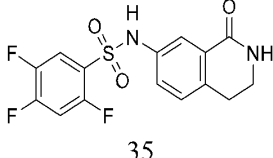
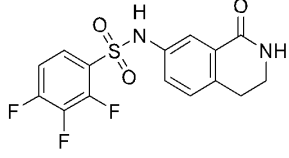
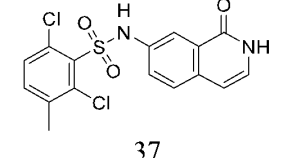
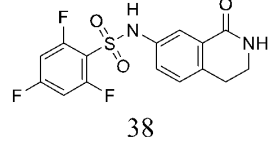
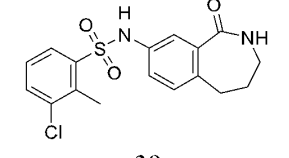
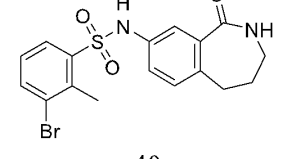
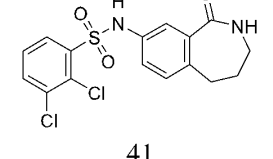
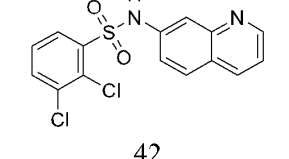
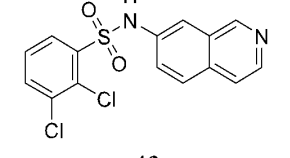
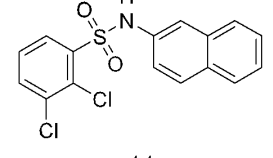
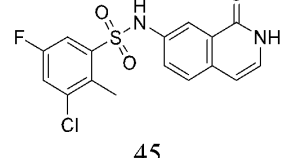
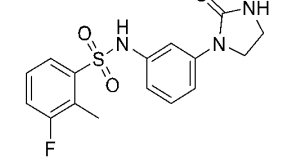
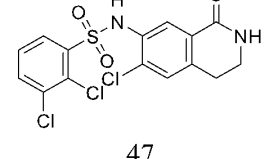
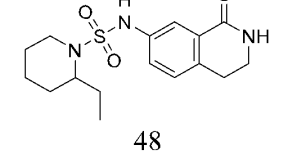
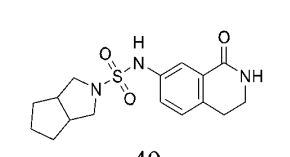
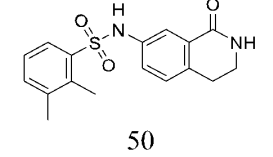
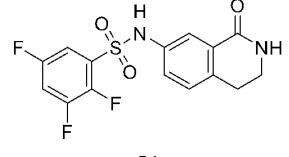
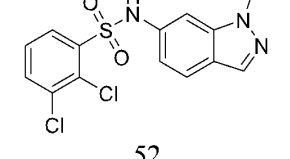
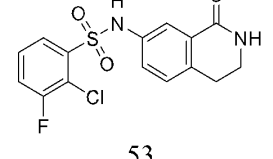
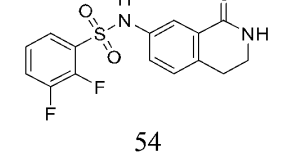
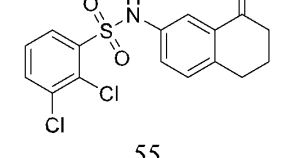
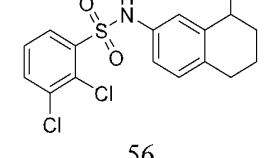
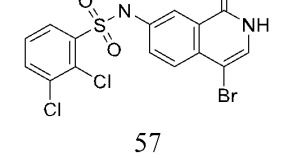


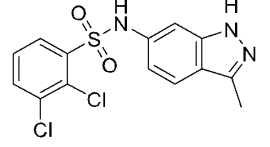
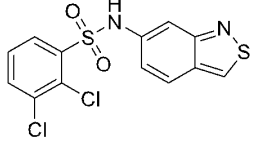
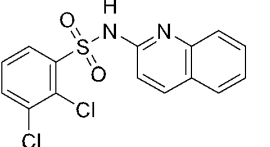
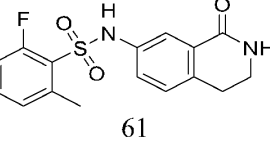
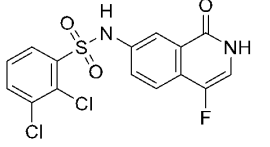
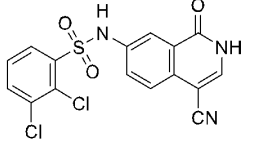
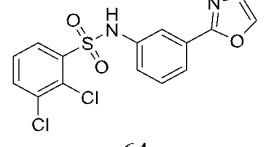
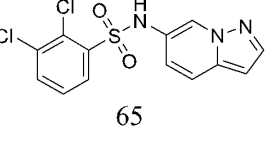
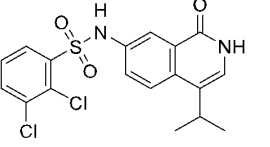
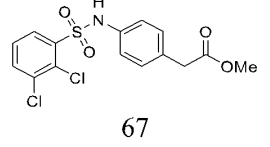
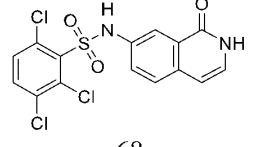
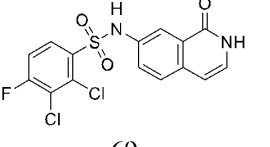
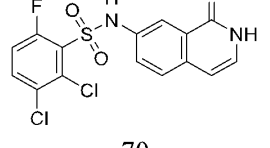
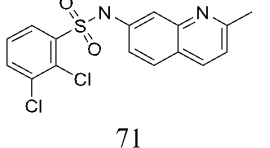
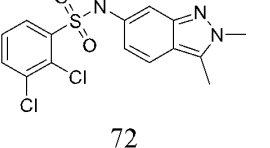
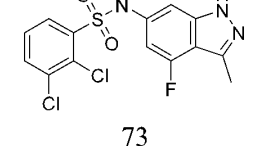
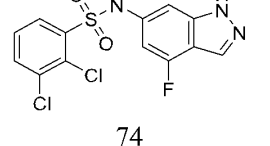
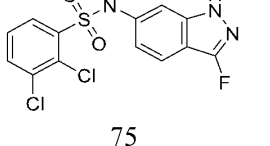
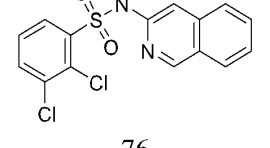
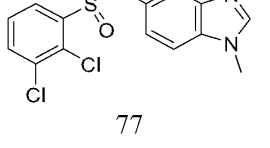
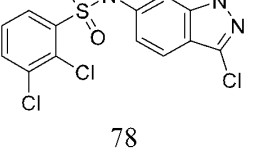
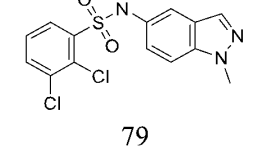
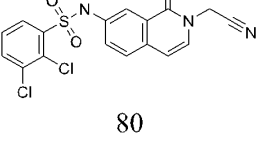
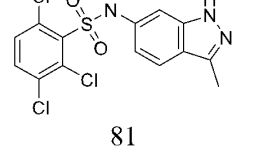
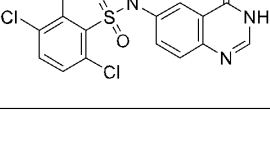
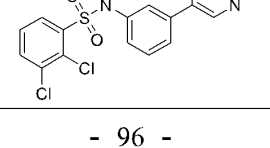
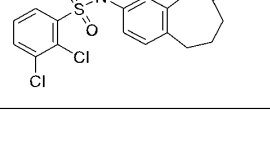
and all other variables not specifically defined herein are as defined in any one of the suitable preceding embodiments.

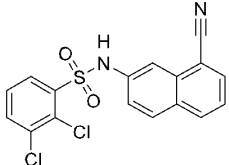
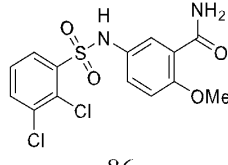
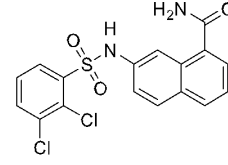
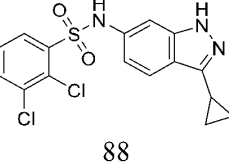
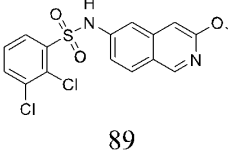
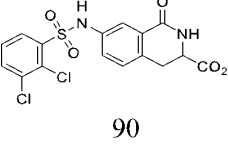
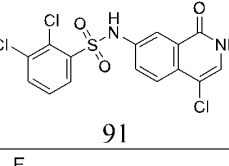
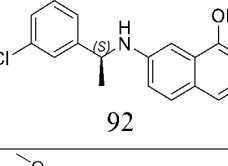
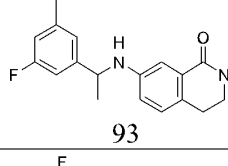
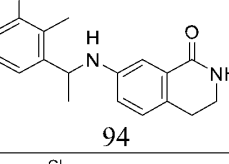
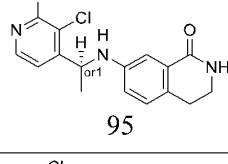
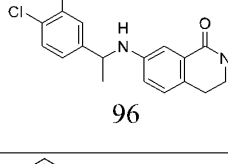
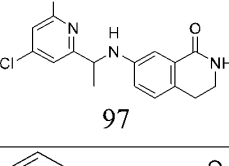
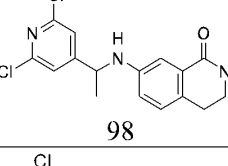
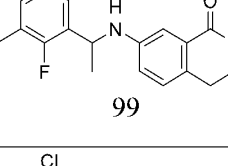
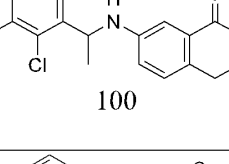
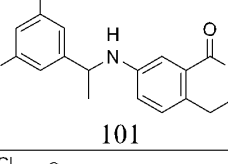
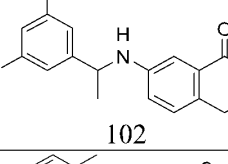
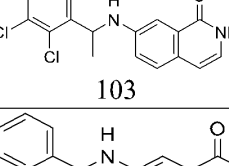
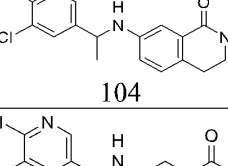
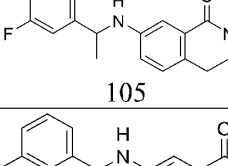
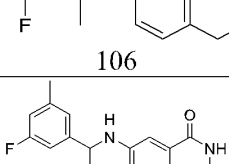
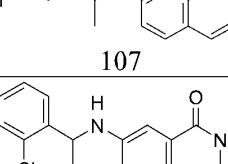
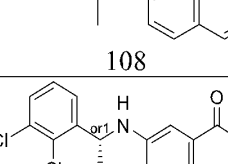
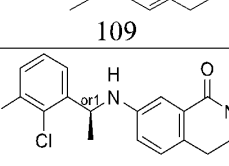
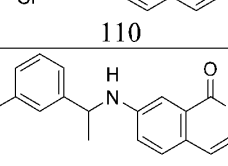
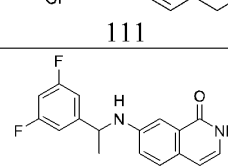
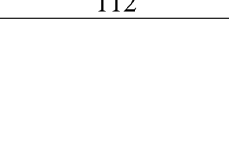
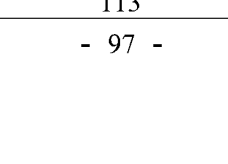
[00191] In a 68th embodiment, in a compound, tautomer, a solvate or stereoisomer
5 of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, L

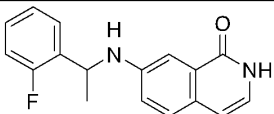
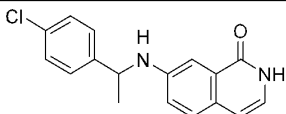
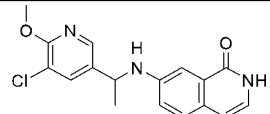
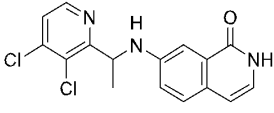
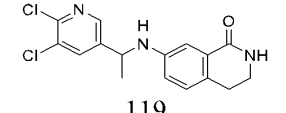
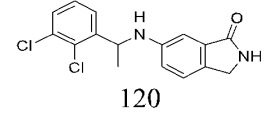
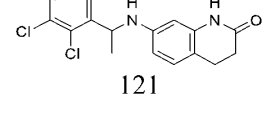
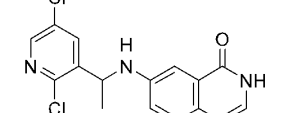
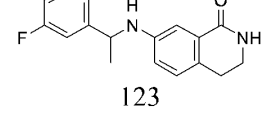
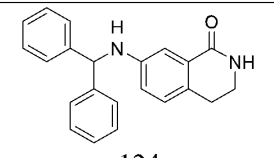
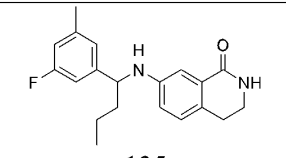
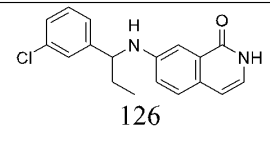
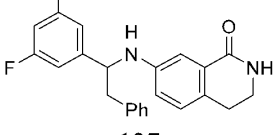
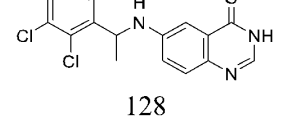
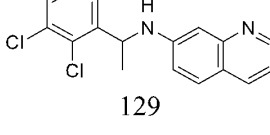
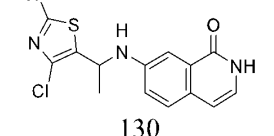
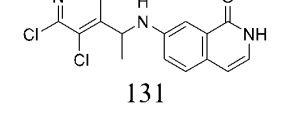
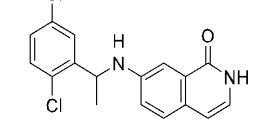
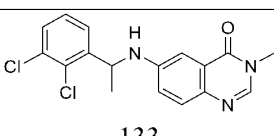
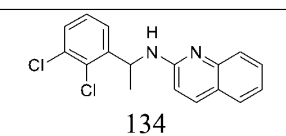
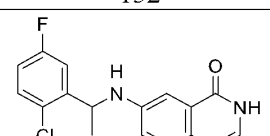
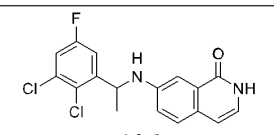
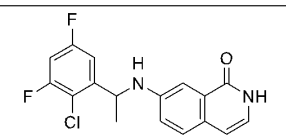
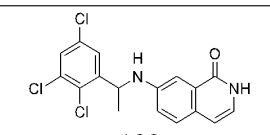
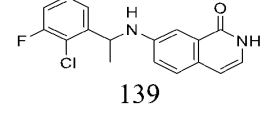
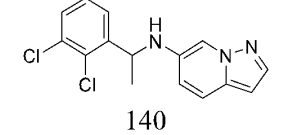
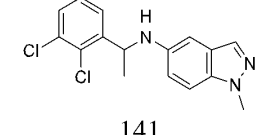


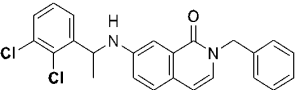
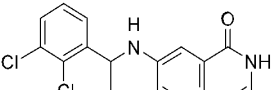
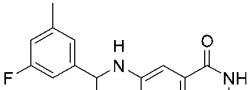
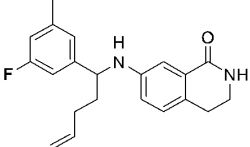
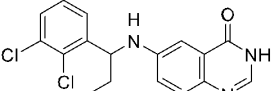
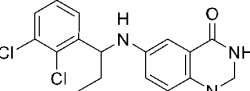
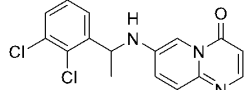
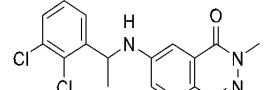
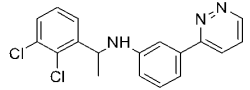
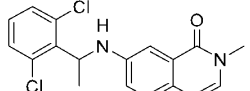
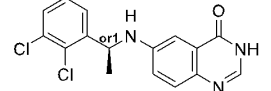
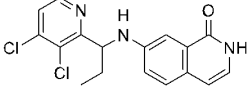
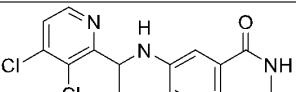
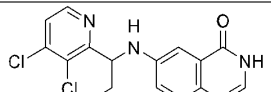
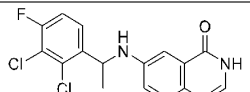
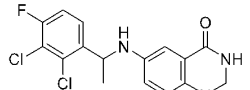
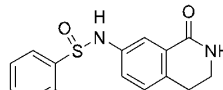
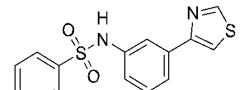
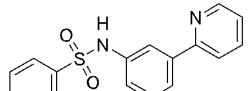
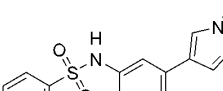
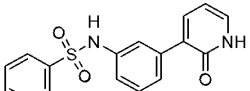
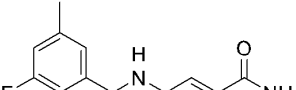
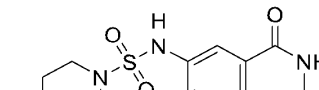
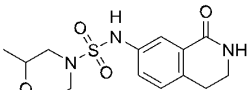
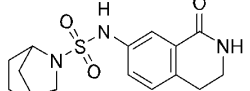
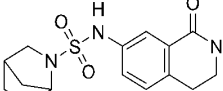
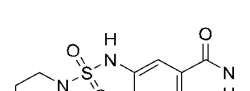
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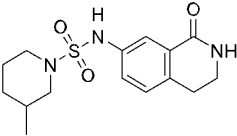
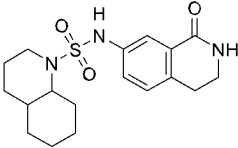
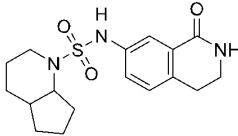
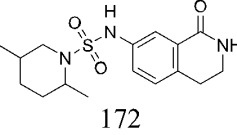
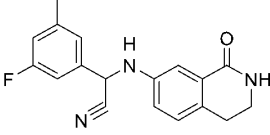
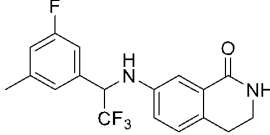
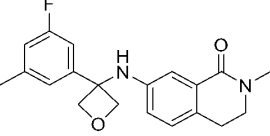
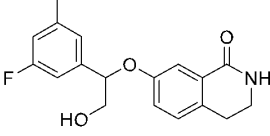
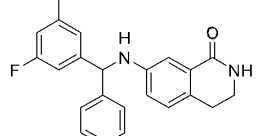
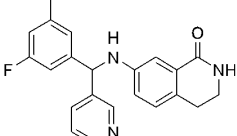
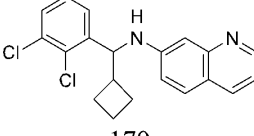
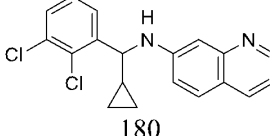
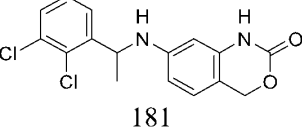
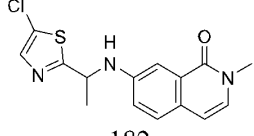
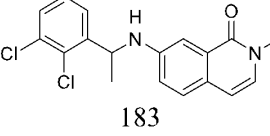
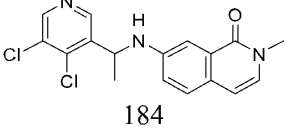
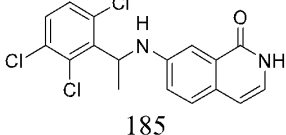
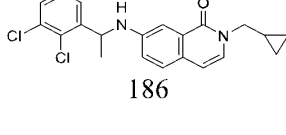
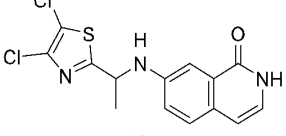
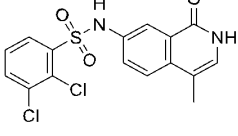
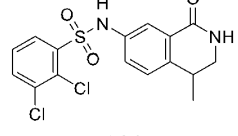
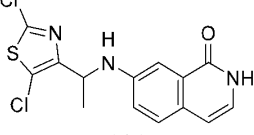
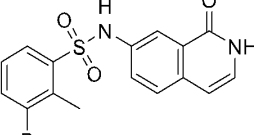
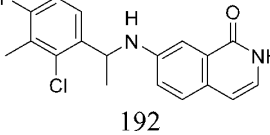
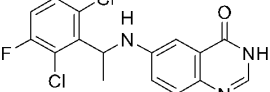
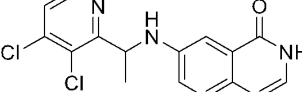
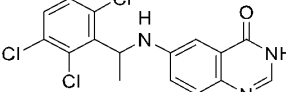
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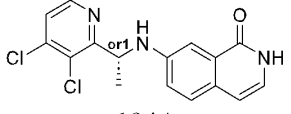
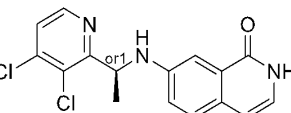
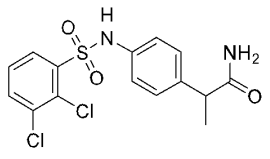
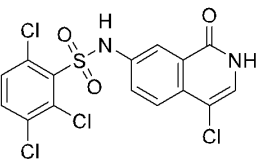
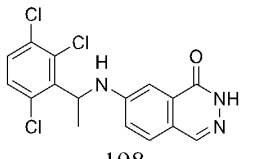
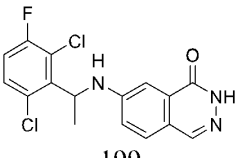
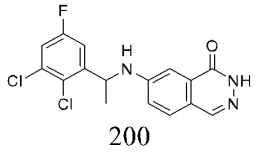
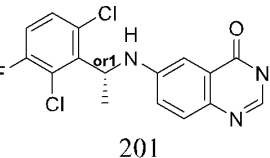
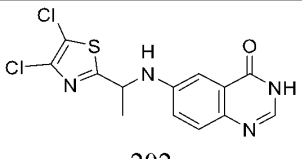
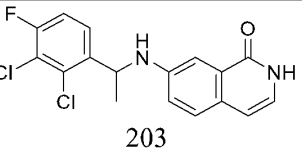
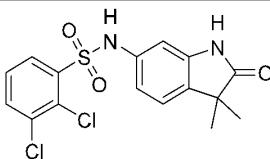
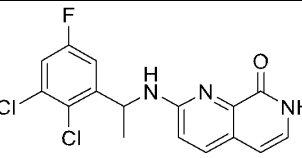
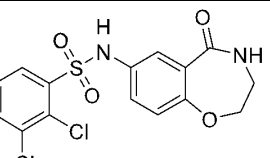
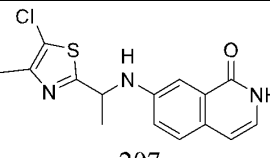
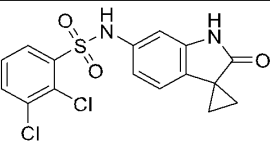
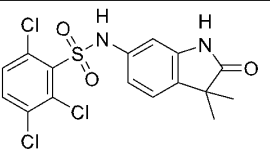
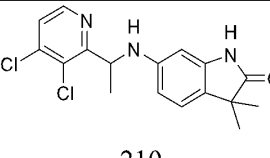
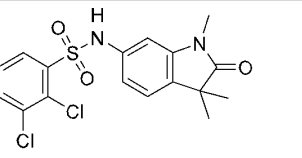
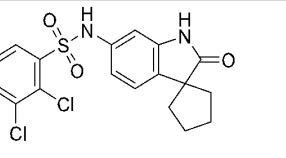
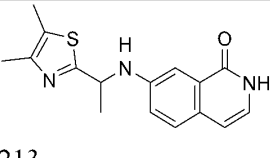
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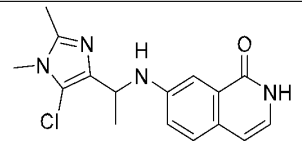
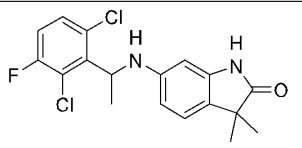
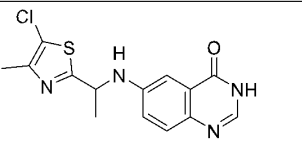
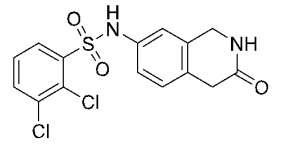
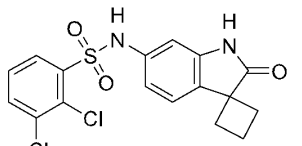
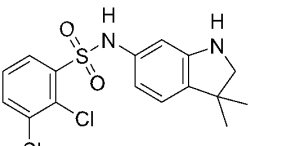
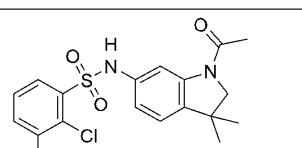
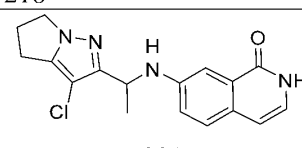
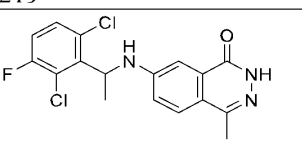
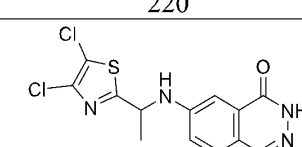
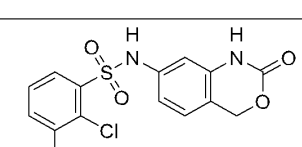
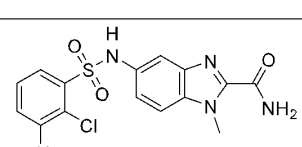
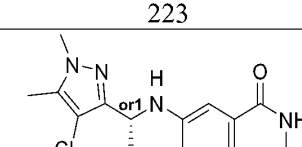
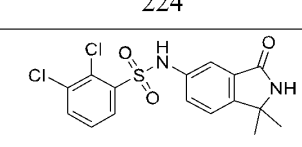
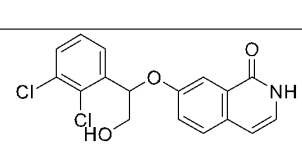
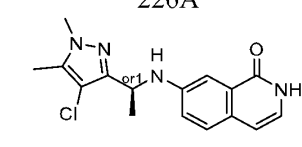
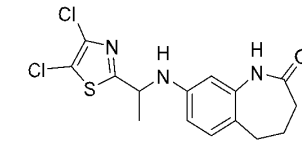
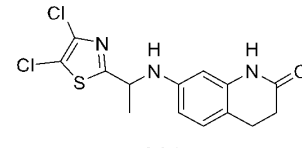
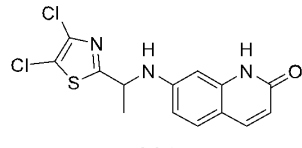
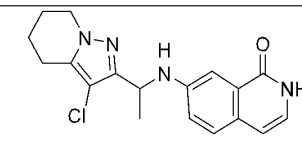
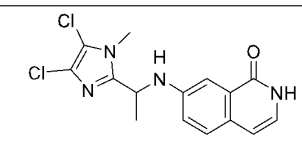
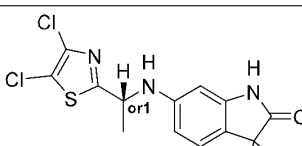
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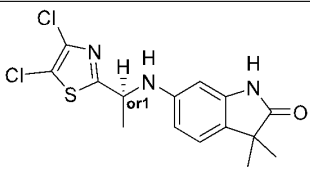
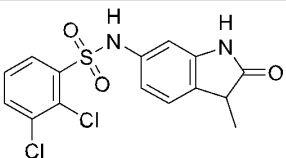
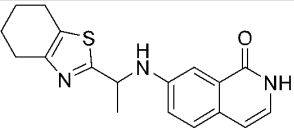
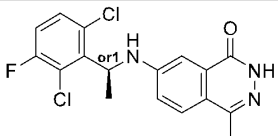
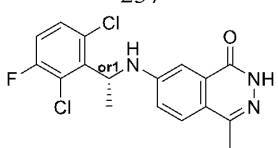
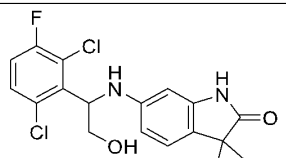
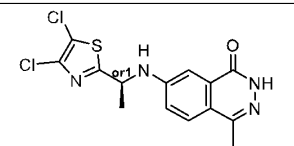
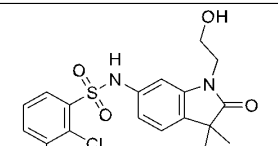
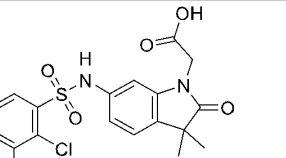
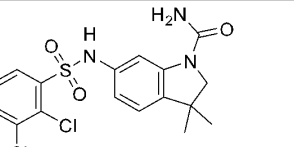
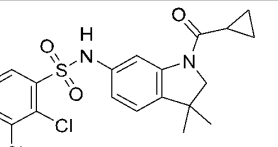
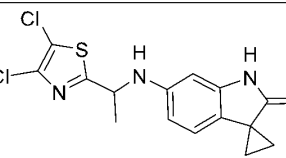
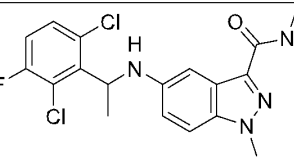
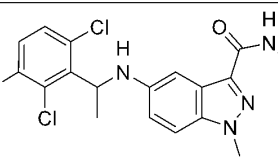
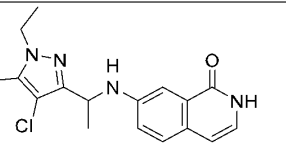
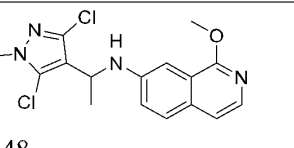
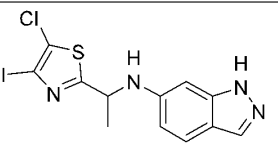
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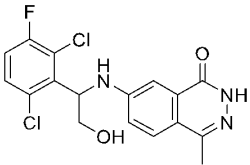
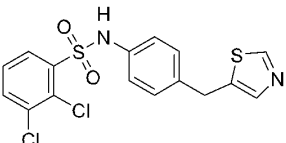
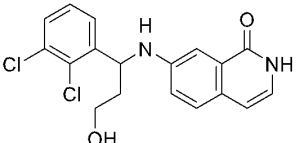
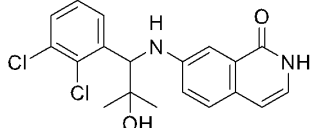
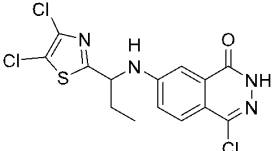
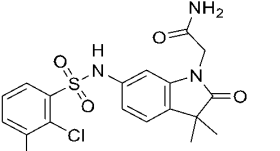
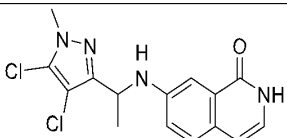
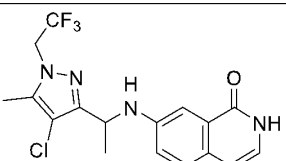
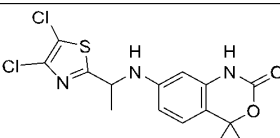
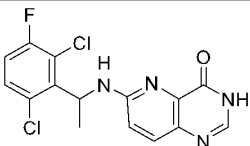
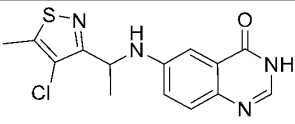
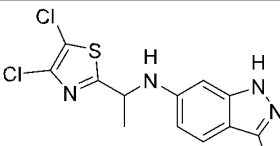
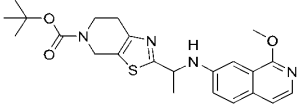
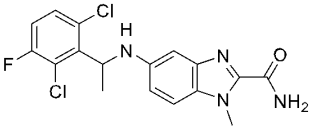
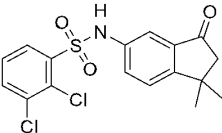
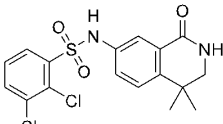
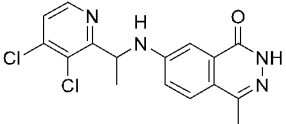
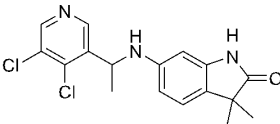
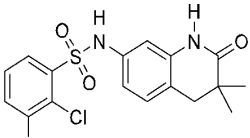
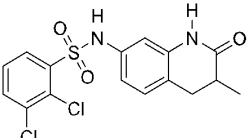
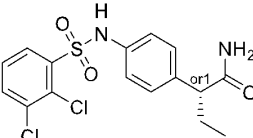
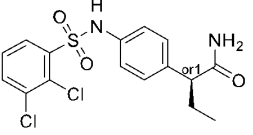
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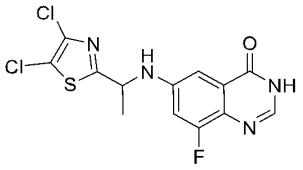
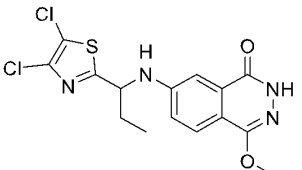
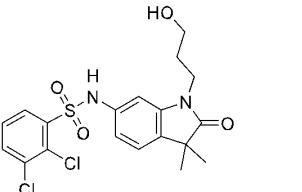
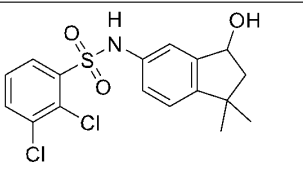
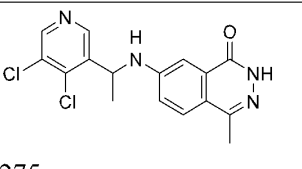
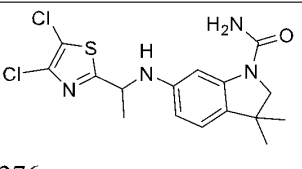
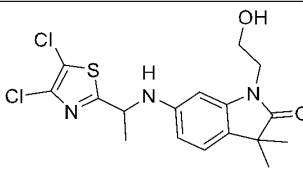
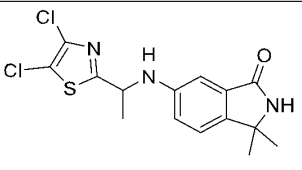
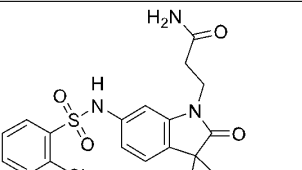
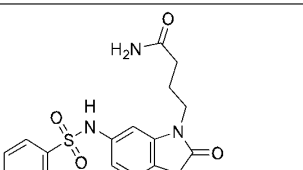
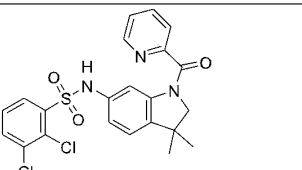
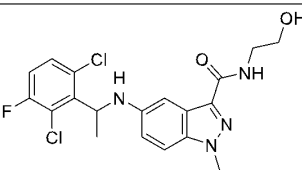
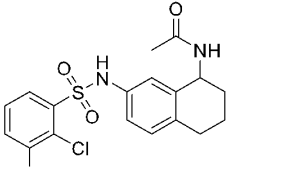
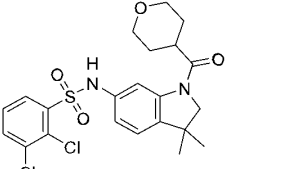
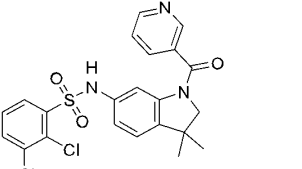
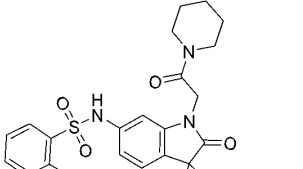
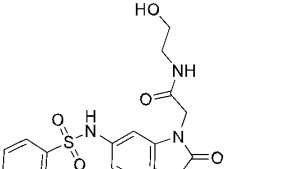
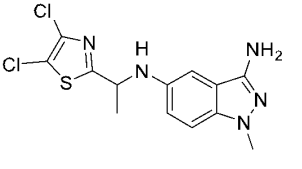
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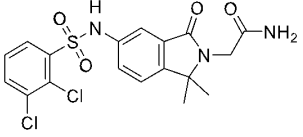
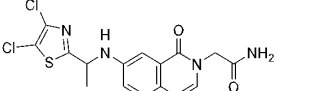
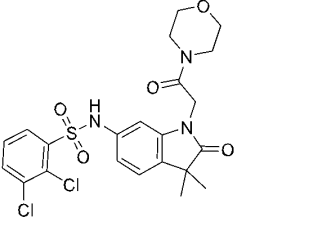
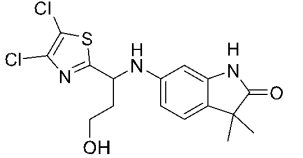
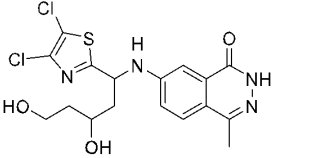
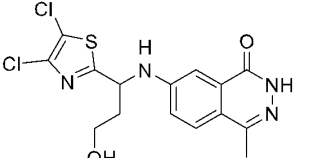
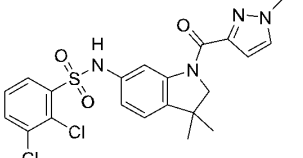
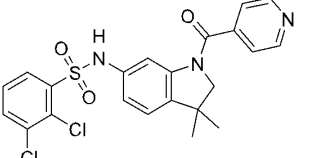
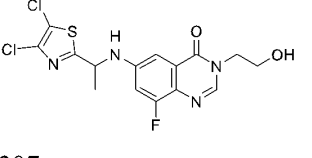
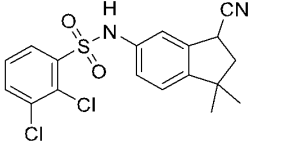
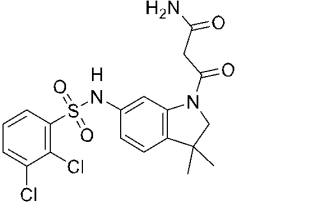
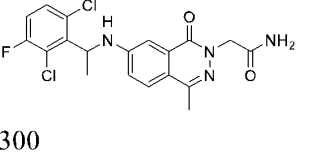
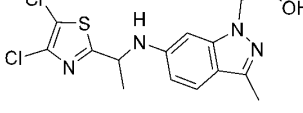
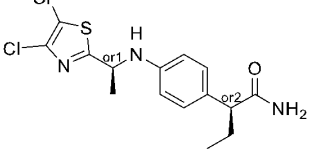
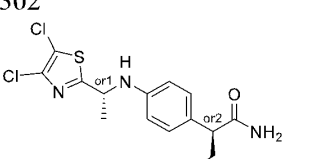
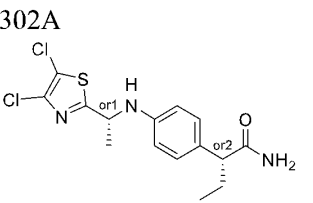
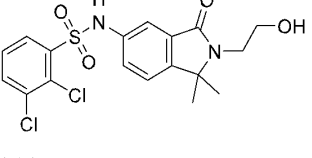
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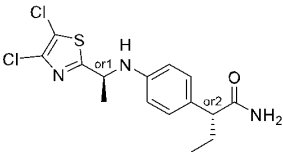
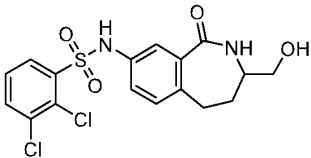
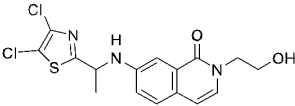
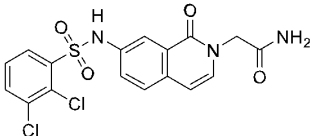
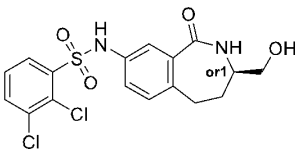
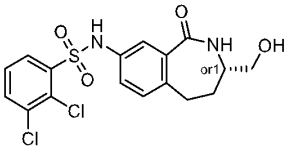
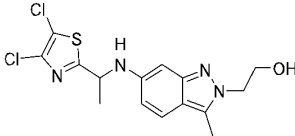
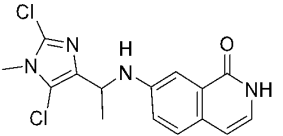
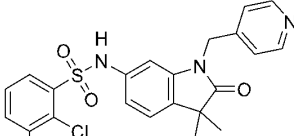
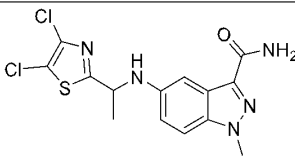
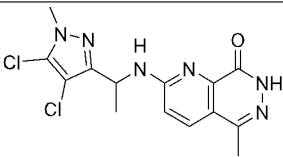
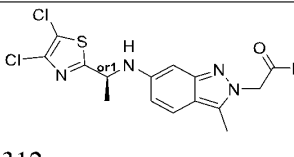
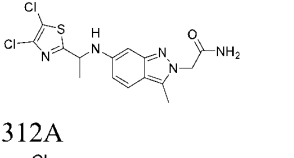
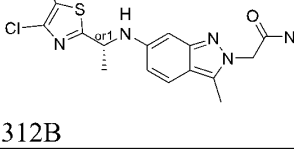
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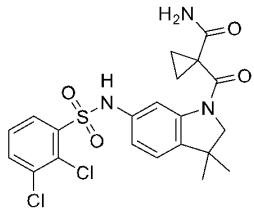
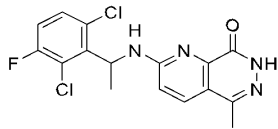
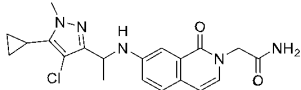
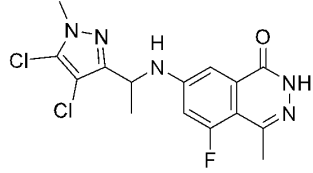
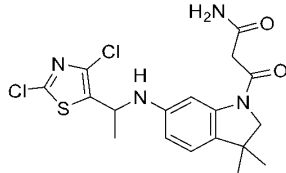
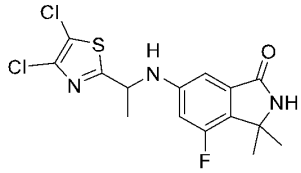
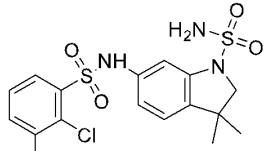
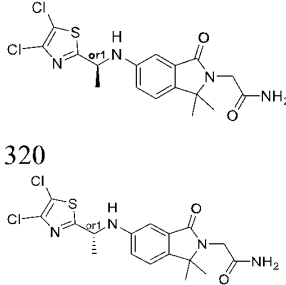
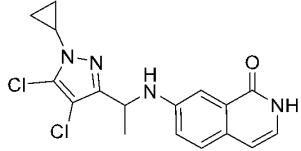
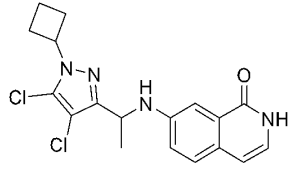
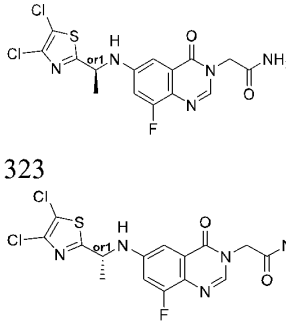
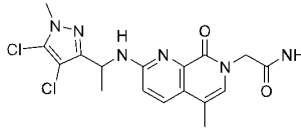
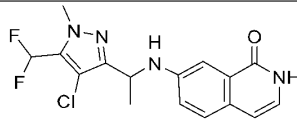
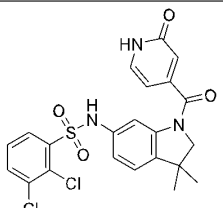
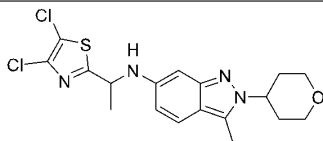
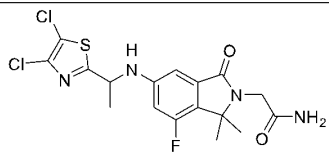
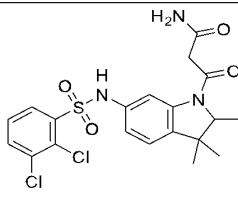
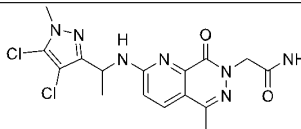
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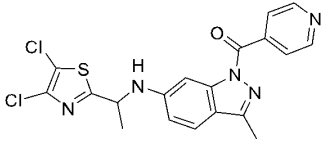
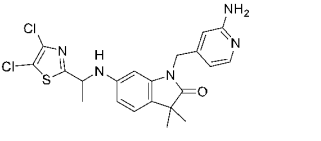
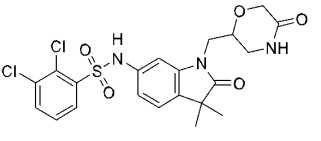
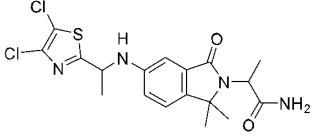
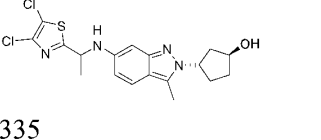
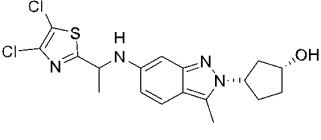
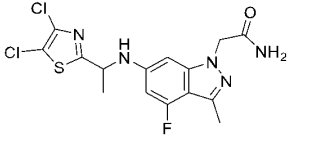
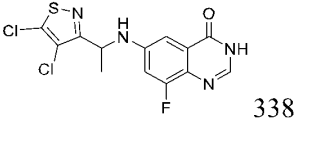
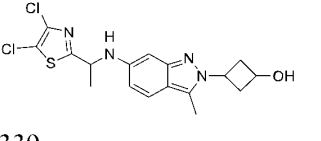
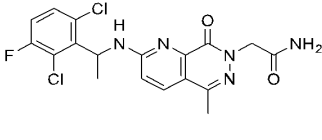
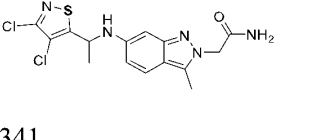
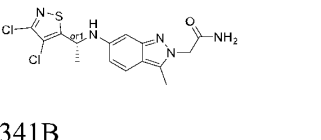
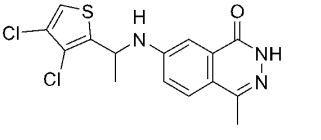
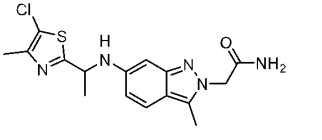
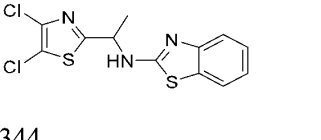
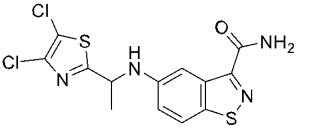
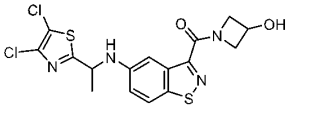
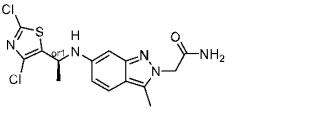
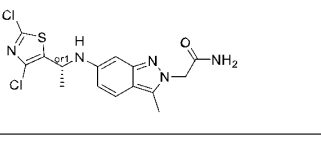
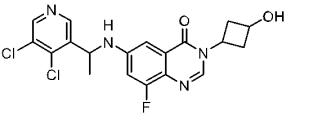
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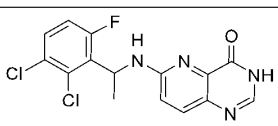
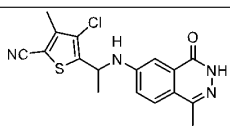
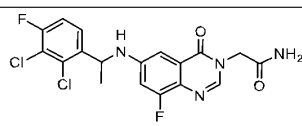
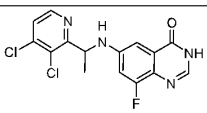
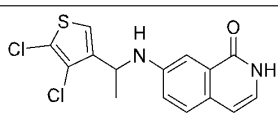
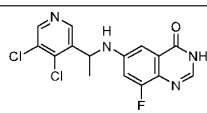
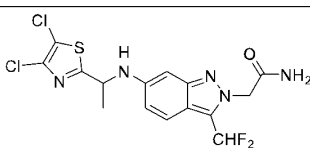
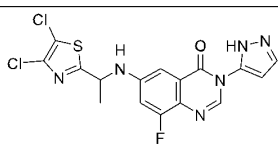
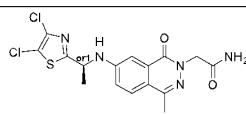
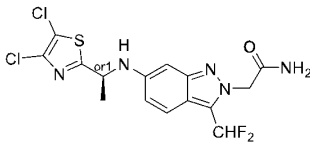
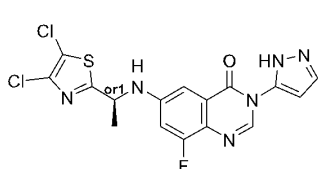
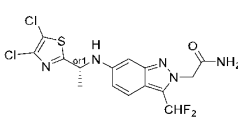
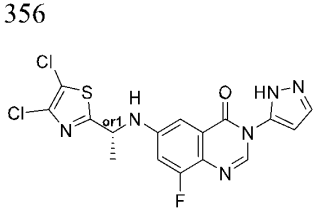
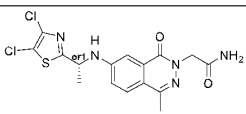
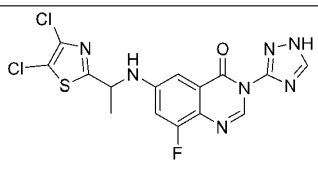
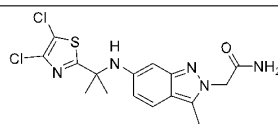
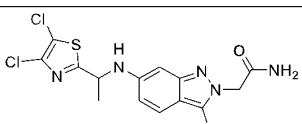
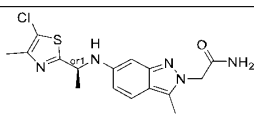
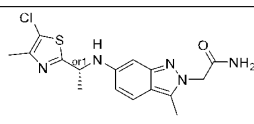
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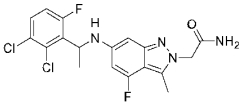
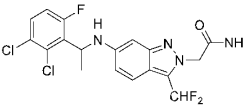
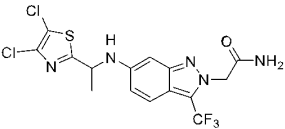
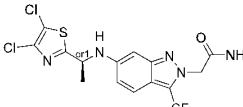
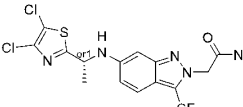
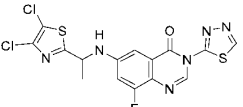
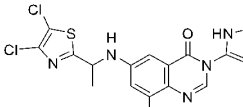
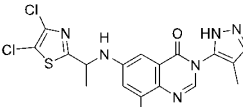
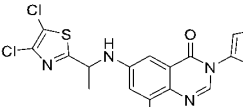
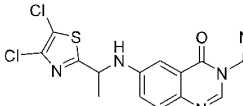
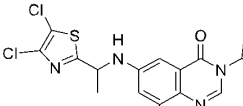
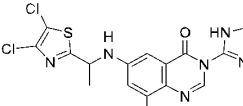
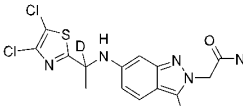
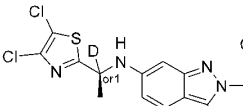
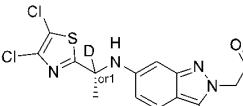
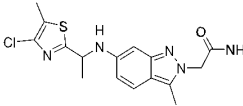
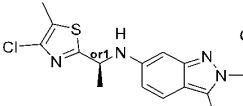
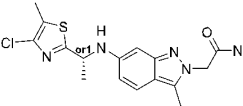
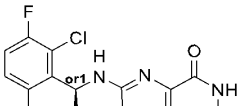
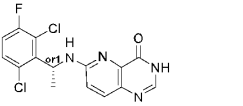
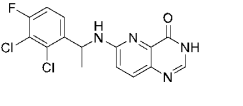
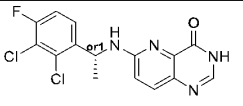
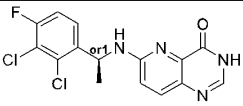
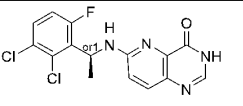
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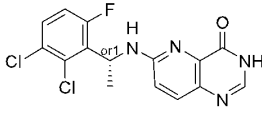
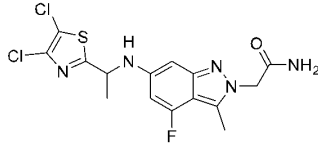
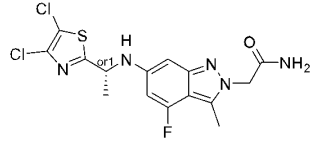
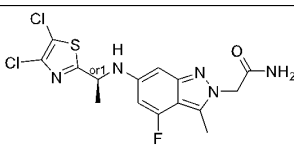
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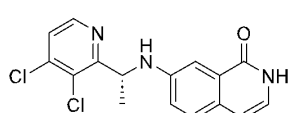
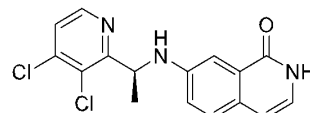
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 355B	 356A	
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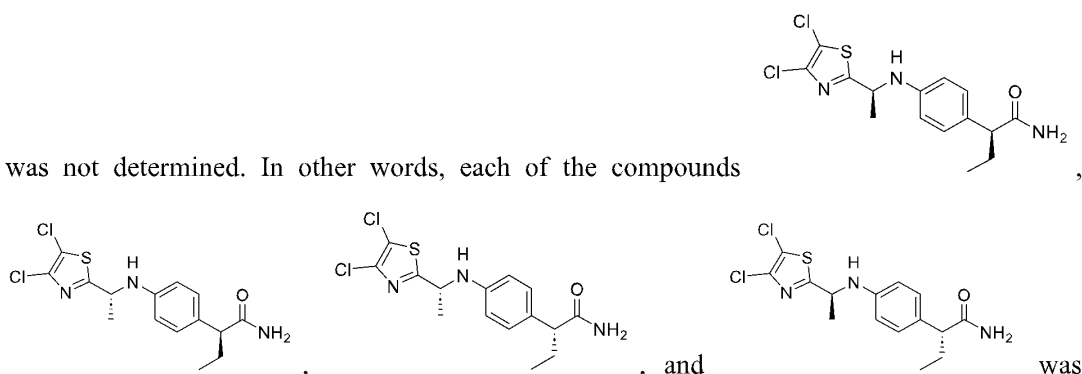
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[00193] The notation “or1” or “or2” as used in chemical structures herein mean that the stereo configuration of the chiral center labeled by “or1” or “or2” is of either R-configuration or S-configuration. For example, Compounds 194A and 194B has an “or1” positioned above the stereo center attached to a methyl group and a hydrogen atom (hydrogen atom not shown). This means that the stereo configuration of the chiral carbon in Compounds 194A and 194B labeled by “or1” is either R or S. Single stereoisomers, i.e., a compound having an R-configuration and a compound having an S-configuration, were separately obtained and characterized by NMR, MS, and retention time, but the stereo configuration of the chiral center was not determined. In

10 other words, each of the compounds  and  was separately obtained as a single stereoisomer. In such cases, the compounds (e.g., Compounds 194A and 194B) are indicated as “Single Unknown Stereoisomer.”

[00194] For another example, Compounds 302, 302A, 302B, and 302C have an “or1” positioned above one stereo center and an “or2” positioned above another stereo center. This means that the stereo configuration of the two chiral carbons in these compounds labeled by “or1” and “or2” are respectively either R or S. Single stereoisomers, e.g., a compound having an (S, S) configuration, a compound having an (R, S) configuration, a compound having an (R, R) configuration, and a compound having an (S, R) configuration, were separately obtained and characterized by NMR, MS, and retention time, but the stereo configuration of the chiral centers

was not determined. In other words, each of the compounds

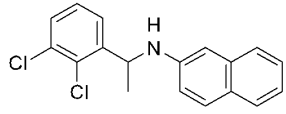
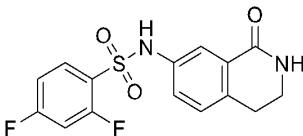
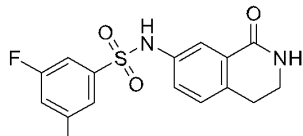
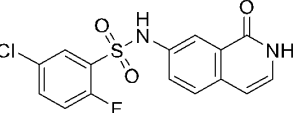
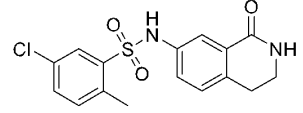
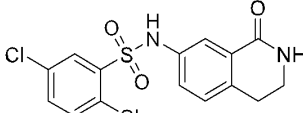
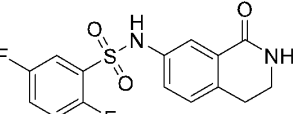
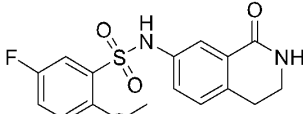
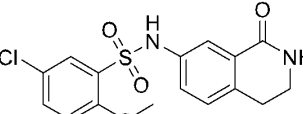
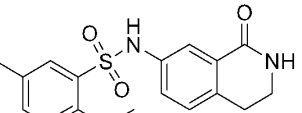
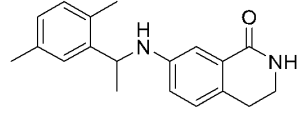
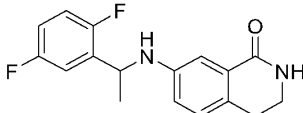
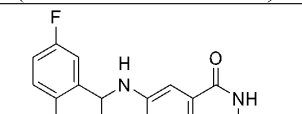
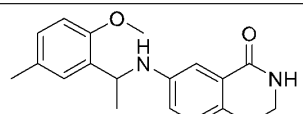
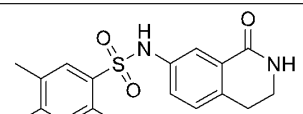
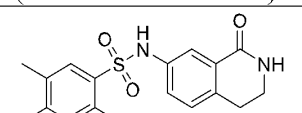
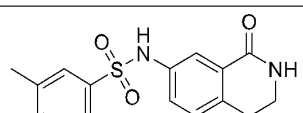
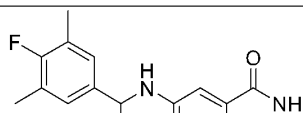
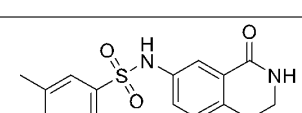
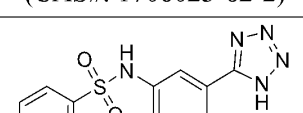
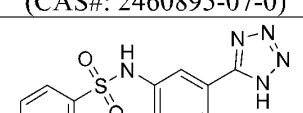


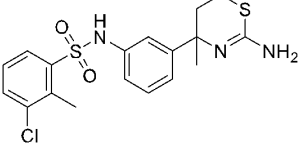
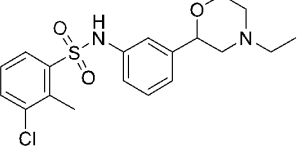
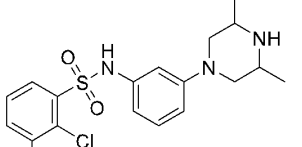
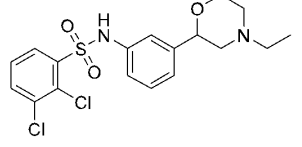
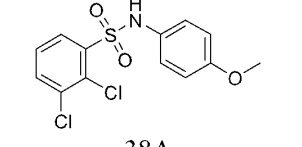
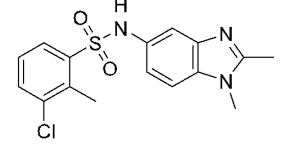
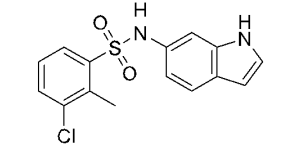
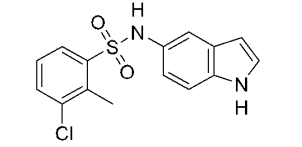
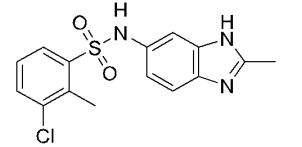
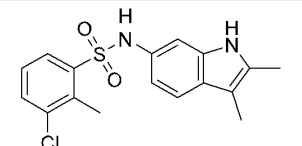
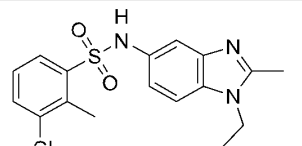
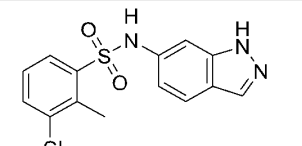
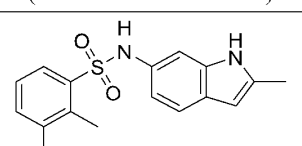
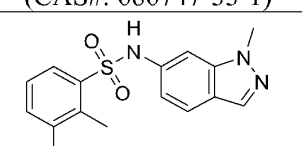
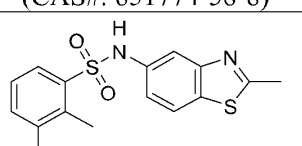
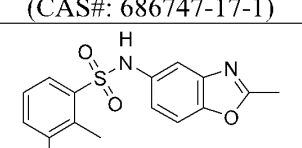
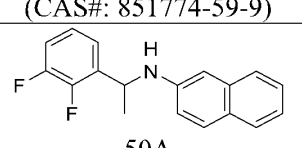
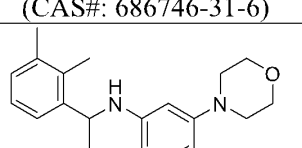
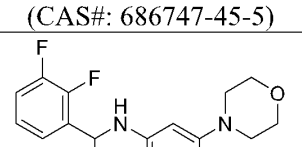
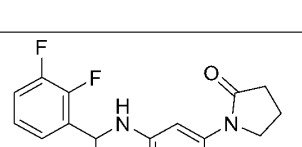
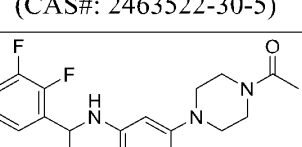
separately obtained as a single stereoisomer.

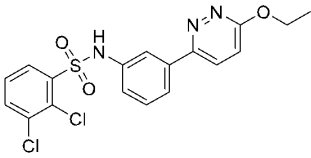
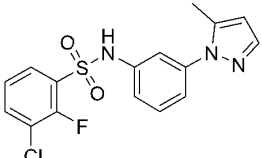
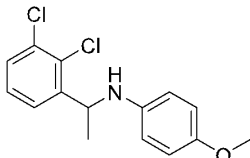
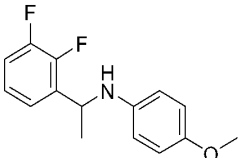
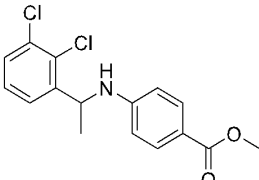
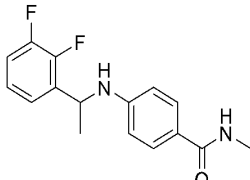
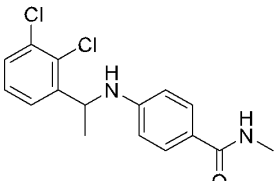
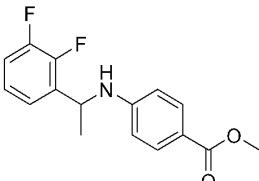
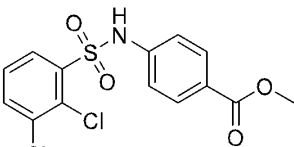
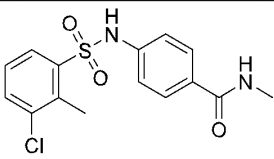
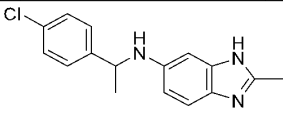
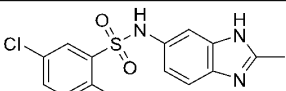
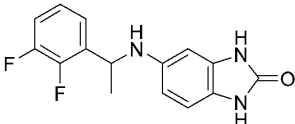
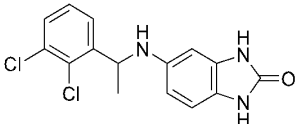
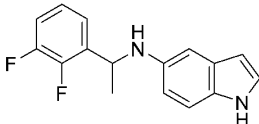
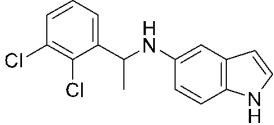
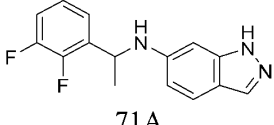
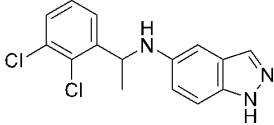
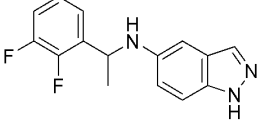
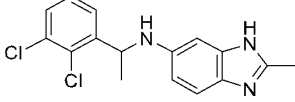
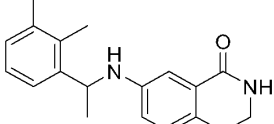
[00195] In certain embodiments, e.g., in embodiments of various uses and methods, a
 5 compound of the disclosure is selected from Compounds 1A to 121A depicted in Table 2, a
 tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a
 pharmaceutically acceptable salt of the foregoing.

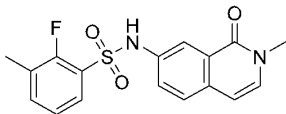
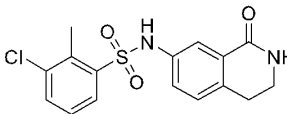
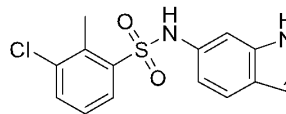
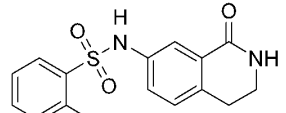
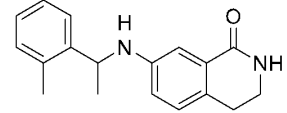
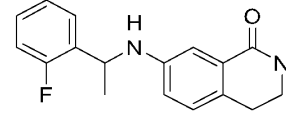
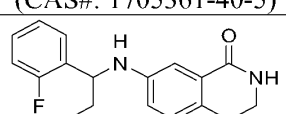
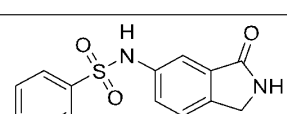
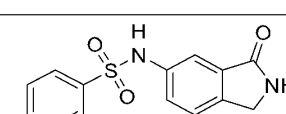
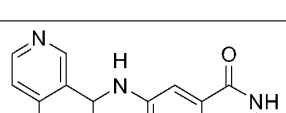
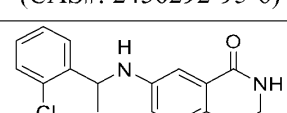
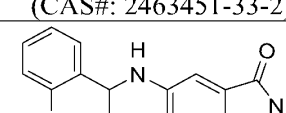
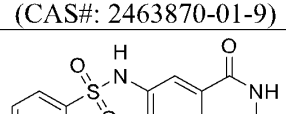
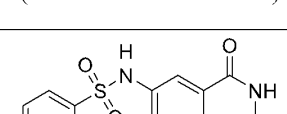
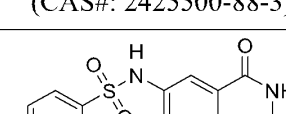
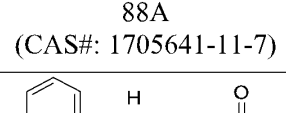
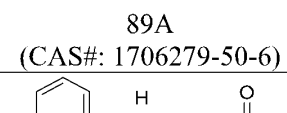
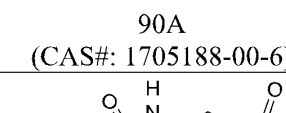
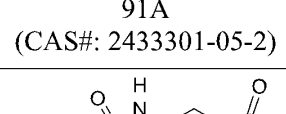
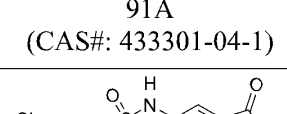
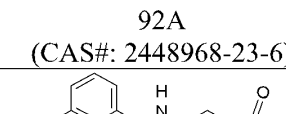
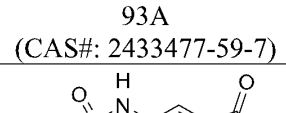
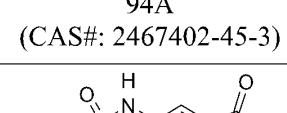
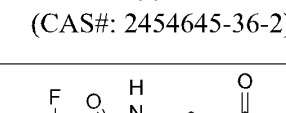
Table 2 Compounds 1A to 121A

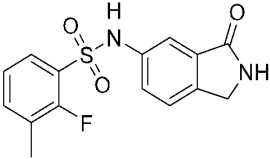
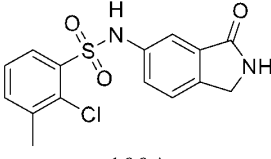
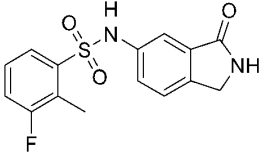
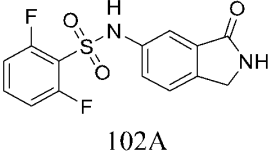
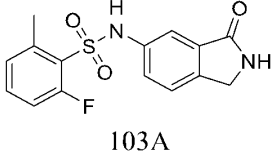
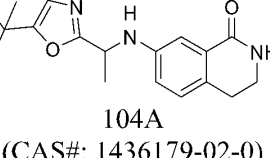
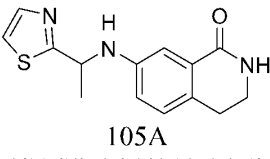
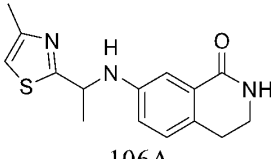
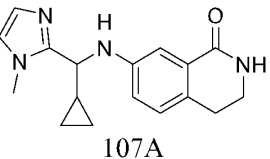
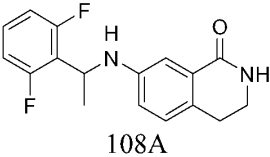
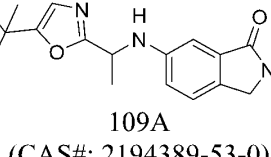
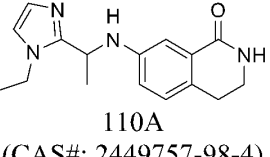
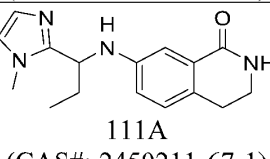
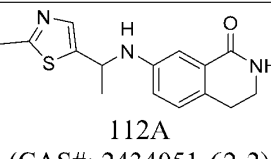
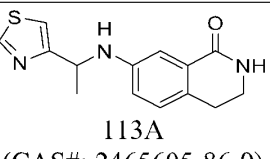
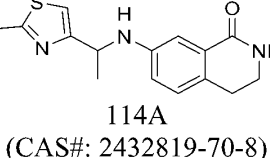
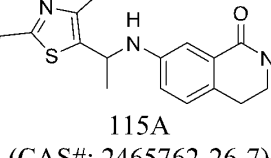
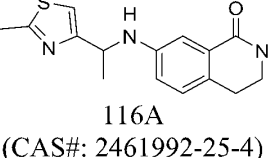
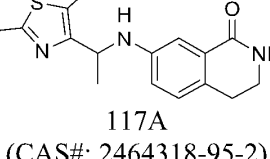
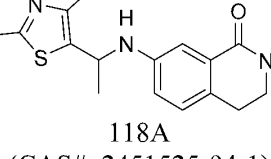
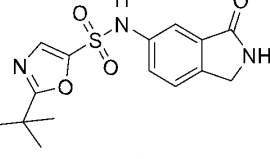
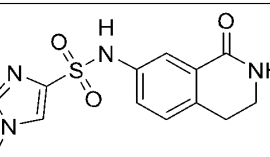
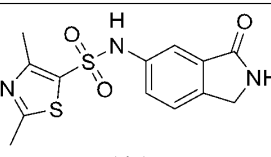
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7A (CAS#: 2454280-07-8)	8A (CAS#: 1427646-07-8)	9A (CAS#: 1705418-11-6)
10A (CAS#: 1706279-52-8)	11A (CAS#: 778621-41-3)	12A (CAS#: 1962748-80-6)

 13A (CAS#: 1944445-67-3)	 14A (CAS#: 1705360-93-5)	 15A (CAS#: 1427966-15-1)
 16A (CAS#: 2728615-72-1)	 17A (CAS#: 1706279-68-6)	 18A (CAS#: 1705439-87-7)
 19A (CAS#: 1705418-03-6)	 20A (CAS#: 1705944-56-4)	 21A (CAS#: 1705439-77-5)
 22A (CAS#: 1704547-35-2)	 23A (CAS#: 2434477-39-9)	 24A (CAS#: 2450195-53-4)
 25A (CAS#: 2433443-40-2)	 26A (CAS#: 2457156-85-1)	 27A (CAS#: 1705188-07-3)
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 64A (CAS#: 1387358-31-7)	 65A (CAS#: 1157743-00-4)	 66A (CAS#: 1232798-27-4)
 67A (CAS#: 1939247-11-6)	 68A (CAS#: 1937182-90-5)	 69A (CAS#: 1963070-36-1)
 70A (CAS#: 1933996-67-8)	 71A (CAS#: 1934013-16-7)	 72A (CAS#: 1933996-75-8)
 73A (CAS#: 1916021-89-0)	 74A (CAS#: 1963742-47-3)	 75A (CAS#: 2467467-72-5)

 76A (CAS#: 2728281-62-5)	 77A (CAS#: 1351658-76-8)	 78A (CAS#: 2326619-66-1)
 79A (CAS#: 1705361-40-5)	 80A (CAS#: 2467870-05-7)	 81A (CAS#: 2461467-89-8)
 82A (CAS#: 2461340-71-4)	 83A (CAS#: 2456292-95-6)	 84A (CAS#: 2463451-33-2)
 85A (CAS#: 2463870-01-9)	 86A (CAS#: 2435425-21-9)	 87A (CAS#: 2425500-88-3)
 88A (CAS#: 1705641-11-7)	 89A (CAS#: 1706279-50-6)	 90A (CAS#: 1705188-00-6)
 91A (CAS#: 2433301-05-2)	 91A (CAS#: 433301-04-1)	 92A (CAS#: 2448968-23-6)
 93A (CAS#: 2433477-59-7)	 94A (CAS#: 2467402-45-3)	 95A (CAS#: 2454645-36-2)
 96A (CAS#: 2466848-89-3)	 97A (CAS#: 2465216-83-3)	 98A (CAS#: 1704990-27-1)

 99A (CAS#: 2464812-26-6)	 100A (CAS#: 2460506-04-9)	 101A (CAS#: 2460011-37-2)
 102A (CAS#: 2461809-09-4)	 103A (CAS#: 2464869-08-5)	 104A (CAS#: 1436179-02-0)
 105A (CAS#: 2464319-24-0)	 106A (CAS#: 2461452-75-3)	 107A (CAS#: 2461789-68-2)
 108A (CAS#: 2430423-95-1)	 109A (CAS#: 2194389-53-0)	 110A (CAS#: 2449757-98-4)
 111A (CAS#: 2450211-67-1)	 112A (CAS#: 2434051-62-2)	 113A (CAS#: 2465605-86-9)
 114A (CAS#: 2432819-70-8)	 115A (CAS#: 2465762-26-7)	 116A (CAS#: 2461992-25-4)
 117A (CAS#: 2464318-95-2)	 118A (CAS#: 2451525-94-1)	 119A (CAS#: 2761522-62-5)
 120A (CAS#: 1428373-70-9)	 121A (CAS#: 2467254-04-0)	

[00196] Another aspect of the disclosure provides a pharmaceutical composition comprising at least one compound selected from a compound of Formulae 1, 2, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2L, 2m, 3, 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3L, 4, 5, 6, 7, 7a, 7b, 8, 8a, 9, 9a, 10, 11, 12, 13, 13a, 13b, 14, 14a, 14b, 14c, 14d, 14e, 14f, 14g, 14h-1, 14h-2, 14i, 14j, 15, 15a, 16-1, 16-2, 16-1a, 16-2a, 17, 17a, 18, 18a, 19, 20, 21, 21a, 21b, 22, 22a, 23, 23a, 24, 25, 26, 27, 28-1, 28-2, 29-1, 29-2, 29-3, 30-1, 30-2, 30-3, 30-4, 30-5, 31-1, 31-2, 32-1, 32-2, 32-3, 32-4, 32-5, 33-1, 33-2, 33-3, 34-1, 34-2, 34-3, 34-4, 34-5, 34-6, 35-1, 35-2, 35-3, 35-4, 36-1, 36-2, 36-3, 37-1, 37-2, 37-3, 37-4, 37-5, 37-6, 38-1, 38-2, 38-3, 39-1, 39-2, 39-3, 39-4, 40-1, 40-2, 40-3, 41-1, 41-2, 41-3, 41-4, 41-5, 42-1, 42-2, 42-3, 43-1, 43-2, 43-3, 43-4, 44-1, 44-2, 44-3, 44-4, 44-5, 44-6, 44-7, 44-8, 44-9, 44-10, 44-11, 44-12, 44-13, 44-14, 45-1, 45-2, 46-1, 46-2, and 46-3 (e.g., Compounds 1 to 391) and Compounds 1A to 121A in Table 2 disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, and at least one pharmaceutically acceptable carrier.

[00197] In some embodiments, the pharmaceutically acceptable carrier is selected from pharmaceutically acceptable vehicles and pharmaceutically acceptable adjuvants. In some embodiments, the pharmaceutically acceptable carrier is chosen from pharmaceutically acceptable fillers, disintegrants, surfactants, binders, and lubricants.

[00198] It will also be appreciated that a pharmaceutical composition of this disclosure can be employed in combination therapies; that is, the pharmaceutical compositions described herein can further include an additional active pharmaceutical agent. Alternatively, a pharmaceutical composition comprising a compound selected from a compound of Formulae 1, 2, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2L, 2m, 3, 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3L, 4, 5, 6, 7, 7a, 7b, 8, 8a, 9, 9a, 10, 11, 12, 13, 13a, 13b, 14, 14a, 14b, 14c, 14d, 14e, 14f, 14g, 14h-1, 14h-2, 14i, 14j, 15, 15a, 16-1, 16-2, 16-1a, 16-2a, 17, 17a, 18, 18a, 19, 20, 21, 21a, 21b, 22, 22a, 23, 23a, 24, 25, 26, 27, 28-1, 28-2, 29-1, 29-2, 29-3, 30-1, 30-2, 30-3, 30-4, 30-5, 31-1, 31-2, 32-1, 32-2, 32-3, 32-4, 32-5, 33-1, 33-2, 33-3, 34-1, 34-2, 34-3, 34-4, 34-5, 34-6, 35-1, 35-2, 35-3, 35-4, 36-1, 36-2, 36-3, 37-1, 37-2, 37-3, 37-4, 37-5, 37-6, 38-1, 38-2, 38-3, 39-1, 39-2, 39-3, 39-4, 40-1, 40-2, 40-3, 41-1, 41-2, 41-3, 41-4, 41-5, 42-1, 42-2, 42-3, 43-1, 43-2, 43-3, 43-4, 44-1, 44-2, 44-3, 44-4, 44-5, 44-6, 44-7, 44-8, 44-9, 44-10, 44-11, 44-12, 44-13, 44-14, 45-1, 45-2, 46-1, 46-2, and 46-3 (e.g., Compounds 1 to 391), and

Compounds 1A to 121A in Table 2 disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing can be administered as a separate composition concurrently with, prior to, or subsequent to, a composition comprising an additional active pharmaceutical agent.

5 [00199] In some embodiments, the pharmaceutically acceptable carrier may be chosen from adjuvants and vehicles. The pharmaceutically acceptable carrier, as used herein, can be chosen, for example, from any and all solvents, diluents, other liquid vehicles, dispersion aids, suspension aids, surface active agents, isotonic agents, thickening agents, emulsifying agents, preservatives, solid binders, and lubricants, which are suited to the
10 particular dosage form desired. Remington: *The Science and Practice of Pharmacy*, 21st edition, 2005, ed. D.B. Troy, Lippincott Williams & Wilkins, Philadelphia, and *Encyclopedia of Pharmaceutical Technology*, eds. J. Swarbrick and J. C. Boylan, 1988 to 1999, Marcel Dekker, New York discloses various carriers used in formulating pharmaceutical compositions and known techniques for the preparation thereof. Except
15 insofar as any conventional carrier is incompatible with the compounds of this disclosure, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition, its use is contemplated to be within the scope of this disclosure. Non-limiting examples of suitable pharmaceutically acceptable carriers include ion exchangers, alumina, aluminum stearate,
20 lecithin, serum proteins (such as human serum albumin), buffer substances (such as phosphates, glycine, sorbic acid, and potassium sorbate), partial glyceride mixtures of saturated vegetable fatty acids, water, salts, and electrolytes (such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, and zinc salts), colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes,
25 polyethylene-polyoxypropylene-block polymers, wool fat, sugars (such as lactose, glucose and sucrose), starches (such as corn starch and potato starch), cellulose and its derivatives (such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate), powdered tragacanth, malt, gelatin, talc, excipients (such as cocoa butter and suppository waxes), oils (such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean
30 oil), glycols (such as propylene glycol and polyethylene glycol), esters (such as ethyl oleate and ethyl laurate), agar, buffering agents (such as magnesium hydroxide and aluminum hydroxide), alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl

alcohol, phosphate buffer solutions, non-toxic compatible lubricants (such as sodium lauryl sulfate and magnesium stearate), coloring agents, releasing agents, coating agents, sweetening agents, flavoring agents, perfuming agents, preservatives, and antioxidants.

[00200] A compound selected from a compound of Formulae 1, 2, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2L, 2m, 3, 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3L, 4, 5, 6, 7, 7a, 7b, 8, 8a, 9, 9a, 10, 11, 12, 13, 13a, 13b, 14, 14a, 14b, 14c, 14d, 14e, 14f, 14g, 14h-1, 14h-2, 14i, 14j, 15, 15a, 16-1, 16-2, 16-1a, 16-2a, 17, 17a, 18, 18a, 19, 20, 21, 21a, 21b, 22, 22a, 23, 23a, 24, 25, 26, 27, 28-1, 28-2, 29-1, 29-2, 29-3, 30-1, 30-2, 30-3, 30-4, 30-5, 31-1, 31-2, 32-1, 32-2, 32-3, 32-4, 32-5, 33-1, 33-2, 33-3, 34-1, 34-2, 34-3, 34-4, 34-5, 34-6, 35-1, 35-2, 35-3, 35-4, 36-1, 36-2, 36-3, 37-1, 37-2, 37-3, 37-4, 37-5, 37-6, 38-1, 38-2, 38-3, 39-1, 39-2, 39-3, 39-4, 40-1, 40-2, 40-3, 41-1, 41-2, 41-3, 41-4, 41-5, 42-1, 42-2, 42-3, 43-1, 43-2, 43-3, 43-4, 44-1, 44-2, 44-3, 44-4, 44-5, 44-6, 44-7, 44-8, 44-9, 44-10, 44-11, 44-12, 44-13, 44-14, 45-1, 45-2, 46-1, 46-2, and 46-3 (e.g., Compounds 1 to 391), and Compounds 1A to 121A in Table 2 disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition disclosed herein can be administered orally in solid dosage forms, such as capsules, tablets, troches, dragées, granules and powders, or in liquid dosage forms, such as elixirs, syrups, emulsions, dispersions, and suspensions. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein can also be administered parenterally, in sterile liquid dosage forms, such as dispersions, suspensions or solutions. Other dosages forms that can also be used to administer the compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein as an ointment, cream, drops, transdermal patch or powder for topical administration, as an ophthalmic solution or suspension formation, e.g., eye drops, for ocular administration, as an aerosol spray or powder composition for inhalation or intranasal administration, or as a cream, ointment, spray or suppository for rectal or vaginal administration.

[00201] Gelatin capsules containing a compound, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, and/or a pharmaceutically acceptable salt of the foregoing disclosed herein and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like, can also be used. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of time.

Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

[00202] Liquid dosage forms for oral administration can further comprise at least one
5 agent selected from coloring and flavoring agents to increase patient acceptance.

[00203] In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols can be examples of suitable carriers for parenteral solutions. Solutions for parenteral administration may comprise a water-soluble salt of the at least one compound describe herein, at least one suitable stabilizing
10 agent, and if necessary, at least one buffer substance. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, can be examples of suitable stabilizing agents. Citric acid and its salts and sodium EDTA can also be used as examples of suitable stabilizing agents. In addition, parenteral solutions can further comprise at least one preservative, selected, for example, from benzalkonium chloride, methyl- and propylparaben,
15 and chlorobutanol.

[00204] A pharmaceutically acceptable carrier is, for example, selected from carriers that are compatible with active ingredients of the composition (and in some embodiments, capable of stabilizing the active ingredients) and not deleterious to the subject to be treated. For example, solubilizing agents, such as cyclodextrins (which can form specific, more soluble
20 complexes with the at least one compound and/or at least one pharmaceutically acceptable salt disclosed herein), can be utilized as pharmaceutical excipients for delivery of the active ingredients. Examples of other carriers include colloidal silicon dioxide, magnesium stearate, cellulose, sodium lauryl sulfate, and pigments such as D&C Yellow # 10. Suitable pharmaceutically acceptable carriers are described in *Remington's Pharmaceutical Sciences*, A.
25 Osol.

[00205] For administration by inhalation, the compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or nebulisers. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described
30 herein may also be delivered as powders, which may be formulated, and the powder composition may be inhaled with the aid of an insufflation powder inhaler device. One exemplary delivery system for inhalation can be metered dose inhalation (MDI) aerosol, which may be formulated

as a suspension or solution of a compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein in at least one suitable propellant, selected, for example, from fluorocarbons and hydrocarbons.

[00206] For ocular administration, an ophthalmic preparation may be formulated with
5 an appropriate weight percentage of a solution or suspension of the compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein in an appropriate ophthalmic vehicle, such that the compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein is maintained in contact with the ocular surface for a sufficient time period to allow the compound to penetrate the corneal and internal
10 regions of the eye.

[00207] Useful pharmaceutical dosage-forms for administration of the compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein include, but are not limited to, hard and soft gelatin capsules, tablets, parenteral injectables, and oral suspensions. In some embodiments, the pharmaceutical compositions disclosed herein may be
15 in the form of controlled release or sustained release compositions as known in the art.

[00208] The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include prefilled,
20 premeasured ampules or syringes of the liquid compositions or pills, tablets, capsules, lozenges or the like in the case of solid compositions. In such compositions, the active material is usually a component ranging from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form. Unit dosage formulations are preferably about of 5, 10, 25,
25 50, 100, 250, 500, or 1,000 mg per unit. In a particular embodiment, unit dosage forms are packaged in a multipack adapted for sequential use, such as blisterpack comprising sheets of at least 6, 9 or 12 unit dosage forms.

[00209] In some embodiments, unit capsules can be prepared by filling standard two-piece hard gelatin capsules each with, for example, 100 milligrams of the compound, tautomer,
30 solvate, stereoisomer, or pharmaceutically acceptable salt described herein in powder, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

[00210] In some embodiments, a mixture of the compound, tautomer, solvate,

stereoisomer, or pharmaceutically acceptable salt described herein and a digestible oil such as soybean oil, cottonseed oil or olive oil can be prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

5 [00211] In some embodiments, tablets can be prepared by conventional procedures so that the dosage unit comprises, for example, 100 milligrams of the compound, stereoisomers thereof, or pharmaceutically acceptable salts thereof, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase
10 palatability or delay absorption.

 [00212] In some embodiments, a parenteral composition suitable for administration by injection can be prepared by stirring 1.5% by weight of the compound and/or at least an enantiomer, a diastereoisomer, or pharmaceutically acceptable salt thereof disclosed herein in 10% by volume propylene glycol. The solution is made to the expected volume with water for
15 injection and sterilized.

 [00213] In some embodiment, an aqueous suspension can be prepared for oral administration. For example, each 5 milliliters of an aqueous suspension comprising 100 milligrams of finely divided compound, stereoisomers thereof, or pharmaceutically acceptable salts thereof, 100 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium
20 benzoate, 1.0 grams of sorbitol solution, U.S.P., and 0.025 milliliters of vanillin can be used.

 [00214] The same dosage forms can generally be used when the compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein is administered stepwise or in conjunction with at least one other therapeutic agent. When drugs are administered in physical combination, the dosage form and administration route should be selected depending
25 on the compatibility of the combined drugs. Thus, the term coadministration is understood to include the administration of at least two agents concomitantly or sequentially, or alternatively as a fixed dose combination of the at least two active components.

 [00215] The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt disclosed herein can be administered as the sole active ingredient or in
30 combination with at least one second active ingredient.

 [00216] The compound, tautomer, solvate, or stereoisomer described herein may be used in the aforementioned form or in the form of their pharmaceutically acceptable salts, such

as hydrochlorides, hydrobromides, acetates, sulfates, citrates, carbonates, trifluoroacetates and the like. When the compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein contain relatively acidic functionalities, salts can be obtained by addition of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salts, or the like. When the compound, tautomer, solvate, or stereoisomer described herein contain relatively basic functionalities, salts can be obtained by addition of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galacturonic acids and the like (see, for example, Berge et al., "Pharmaceutical Salts," Journal of Pharmaceutical Science, 1977, 66, 1-19).

[00217] Neutral forms of the pharmaceutically acceptable salt described herein may be regenerated by contacting the salt with a base or acid, and isolating the parent compound in the conventional manner.

[00218] This disclosure provides prodrugs. Prodrugs of the compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein that readily undergo chemical changes under physiological conditions to provide the compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of the present disclosure. Additionally, prodrugs can be converted to the compound, tautomer, solvate, stereoisomer, or a pharmaceutically acceptable salt of the present disclosure by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to the compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of the present disclosure when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be more bioavailable by oral administration than the parent drug. The prodrug may also have improved solubility in pharmacological compositions over the

parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound of the present disclosure which is administered as an ester (the "prodrug"), but then is metabolically hydrolyzed to the carboxylic acid, i.e., the active entity.

5 [00219] Certain compound, tautomer, stereoisomer, or pharmaceutically acceptable salt of the disclosure can exist in unsolvated forms as well as solvated forms, including hydrate forms. Certain compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of the disclosure may exist in multiple crystalline or amorphous forms.

[00220] Certain compound, tautomer, solvate, or pharmaceutically acceptable salt in
10 this disclosure possesses asymmetric carbon atoms (optical centers) or double bonds; the racemates, enantiomers, diastereoisomers, geometric isomers and individual isomers are all intended to be encompassed within the scope of the present disclosure.

III. Methods of Treatment and Uses

[00221] The present disclosure provides methods of treatment and uses utilizing a
15 compound set forth in any one of the various embodiments of Section II (Compounds and Compositions) and Tables 1 and 2, e.g., a compound of Formulae 1, 2, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2L, 2m, 3, 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3L, 4, 5, 6, 7, 7a, 7b, 8, 8a, 9, 9a, 10, 11, 12, 13, 13a, 13b, 14, 14a, 14b, 14c, 14d, 14e, 14f, 14g, 14h-1, 14h-2, 14i, 14j, 15, 15a, 16-1, 16-2, 16-1a, 16-2a, 17, 17a, 18, 18a, 19, 20, 21, 21a, 21b, 22, 22a, 23, 23a, 24, 25, 26,
20 27, 28-1, 28-2, 29-1, 29-2, 29-3, 30-1, 30-2, 30-3, 30-4, 30-5, 31-1, 31-2, 32-1, 32-2, 32-3, 32-4, 32-5, 33-1, 33-2, 33-3, 34-1, 34-2, 34-3, 34-4, 34-5, 34-6, 35-1, 35-2, 35-3, 35-4, 36-1, 36-2, 36-3, 37-1, 37-2, 37-3, 37-4, 37-5, 37-6, 38-1, 38-2, 38-3, 39-1, 39-2, 39-3, 39-4, 40-1, 40-2, 40-3, 41-1, 41-2, 41-3, 41-4, 41-5, 42-1, 42-2, 42-3, 43-1, 43-2, 43-3, 43-4, 44-1, 44-2, 44-3, 44-4, 44-5, 44-6, 44-7, 44-8, 44-9, 44-10, 44-11, 44-12, 44-13, 44-14, 45-1, 45-2, 46-1, 46-2,
25 and 46-3, as well as Compounds 1 to 391 in Table 1 and Compounds 1A to 121A in Table 2, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the compound, tautomer, solvate, stereoisomer, and pharmaceutically acceptable salt.

30 [00222] One aspect of the disclosure provides a method of treating a disease or condition, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of Formulae 1, 2, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2L, 2m, 3, 3a,

3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3L, 4, 5, 6, 7, 7a, 7b, 8, 8a, 9, 9a, 10, 11, 12, 13, 13a, 13b, 14, 14a, 14b, 14c, 14d, 14e, 14f, 14g, 14h-1, 14h-2, 14i, 14j, 15, 15a, 16-1, 16-2, 16-1a, 16-2a, 17, 17a, 18, 18a, 19, 20, 21, 21a, 21b, 22, 22a, 23, 23a, 24, 25, 26, 27, 28-1, 28-2, 29-1, 29-2, 29-3, 30-1, 30-2, 30-3, 30-4, 30-5, 31-1, 31-2, 32-1, 32-2, 32-3, 32-4, 32-5, 33-1, 33-2, 33-3, 34-1, 34-2, 34-3, 34-4, 34-5, 34-6, 35-1, 35-2, 35-3, 35-4, 36-1, 36-2, 36-3, 37-1, 37-2, 37-3, 37-4, 37-5, 37-6, 38-1, 38-2, 38-3, 39-1, 39-2, 39-3, 39-4, 40-1, 40-2, 40-3, 41-1, 41-2, 41-3, 41-4, 41-5, 42-1, 42-2, 42-3, 43-1, 43-2, 43-3, 43-4, 44-1, 44-2, 44-3, 44-4, 44-5, 44-6, 44-7, 44-8, 44-9, 44-10, 44-11, 44-12, 44-13, 44-14, 45-1, 45-2, 46-1, 46-2, and 46-3 (e.g., Compounds 1 to 391), and Compounds 1A to 121A disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the compound, tautomer, solvate, stereoisomer, and pharmaceutically acceptable salt, wherein the disease or condition includes, but is not limited to, amyotrophic lateral sclerosis (ALS), Parkinson's disease, Parkinsonian syndromes, ischemia, stroke, herpes infection, a demyelinating disease such as multiple sclerosis, traumatic brain injury, sepsis, a chronic disease of PNS including inherited neuropathies, such as, but is not limited to Charcot-Marie-Tooth disease and chronic inflammatory demyelinating polyneuropathy (CIDP), an optic nerve disorder such as glaucoma, and retinal ganglion degeneration, colitis, a metabolic disease or disorder such as diabetic neuropathy, nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) and a peripheral neuropathy like CIPN induced by various drugs, such as, but not limited to taxanes, vinca alkaloids and proteasome inhibitors. In some embodiments, the disease or condition is caused by axonal degeneration or neuronal cells damage.

[00223] In another aspect, disclosed herein is a compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt as described herein, including a compound of Formulae 1, 2, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2L, 2m, 3, 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3L, 4, 5, 6, 7, 7a, 7b, 8, 8a, 9, 9a, 10, 11, 12, 13, 13a, 13b, 14, 14a, 14b, 14c, 14d, 14e, 14f, 14g, 14h-1, 14h-2, 14i, 14j, 15, 15a, 16-1, 16-2, 16-1a, 16-2a, 17, 17a, 18, 18a, 19, 20, 21, 21a, 21b, 22, 22a, 23, 23a, 24, 25, 26, 27, 28-1, 28-2, 29-1, 29-2, 29-3, 30-1, 30-2, 30-3, 30-4, 30-5, 31-1, 31-2, 32-1, 32-2, 32-3, 32-4, 32-5, 33-1, 33-2, 33-3, 34-1, 34-2, 34-3, 34-4, 34-5, 34-6, 35-1, 35-2, 35-3, 35-4, 36-1, 36-2, 36-3, 37-1, 37-2, 37-3, 37-4, 37-5, 37-6, 38-1, 38-2, 38-3, 39-1, 39-2, 39-3, 39-4, 40-1, 40-2, 40-3, 41-1, 41-2, 41-3, 41-4, 41-5, 42-1, 42-2,

42-3, 43-1, 43-2, 43-3, 43-4, 44-1, 44-2, 44-3, 44-4, 44-5, 44-6, 44-7, 44-8, 44-9, 44-10, 44-11, 44-12, 44-13, 44-14, 45-1, 45-2, 46-1, 46-2, and 46-3 (e.g., Compounds 1 to 391), and Compounds 1A to 121A disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a
5 pharmaceutical composition comprising any of the compound, tautomer, solvate, stereoisomer, and pharmaceutically acceptable salt, for use as a medicament.

[00224] In another aspect, disclosed herein is use of a compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt as described herein, including a compound of Formulae 1, 2, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2L, 2m, 3, 3a, 3b, 3c, 3d,
10 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3L, 4, 5, 6, 7, 7a, 7b, 8, 8a, 9, 9a, 10, 11, 12, 13, 13a, 13b, 14, 14a, 14b, 14c, 14d, 14e, 14f, 14g, 14h-1, 14h-2, 14i, 14j, 15, 15a, 16-1, 16-2, 16-1a, 16-2a, 17, 17a, 18, 18a, 19, 20, 21, 21a, 21b, 22, 22a, 23, 23a, 24, 25, 26, 27, 28-1, 28-2, 29-1, 29-2, 29-3, 30-1, 30-2, 30-3, 30-4, 30-5, 31-1, 31-2, 32-1, 32-2, 32-3, 32-4, 32-5, 33-1, 33-2, 33-3, 34-1, 34-2, 34-3, 34-4, 34-5, 34-6, 35-1, 35-2, 35-3, 35-4, 36-1, 36-2, 36-3, 37-1, 37-2, 37-3, 37-4, 37-5, 37-6, 38-
15 1, 38-2, 38-3, 39-1, 39-2, 39-3, 39-4, 40-1, 40-2, 40-3, 41-1, 41-2, 41-3, 41-4, 41-5, 42-1, 42-2, 42-3, 43-1, 43-2, 43-3, 43-4, 44-1, 44-2, 44-3, 44-4, 44-5, 44-6, 44-7, 44-8, 44-9, 44-10, 44-11, 44-12, 44-13, 44-14, 45-1, 45-2, 46-1, 46-2, and 46-3 (e.g., Compounds 1 to 391), and Compounds 1A to 121A disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a
20 pharmaceutical composition comprising any of the compound, tautomer, solvate, stereoisomer, and pharmaceutically acceptable salt, for the manufacture of a medicament for treating a disease or condition that includes, but is not limited to, amyotrophic lateral sclerosis (ALS), Parkinson's disease, Parkinsonian syndromes, ischemia, stroke, herpes infection, a demyelinating disease such as multiple sclerosis, traumatic brain injury, sepsis,
25 a chronic disease of PNS including inherited neuropathies, such as, but is not limited to Charcot-Marie-Tooth disease and chronic inflammatory demyelinating polyneuropathy (CIDP), an optic nerve disorder such as glaucoma, and retinal ganglion degeneration, colitis, a metabolic disease or disorder such as diabetic neuropathy, nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) and a peripheral neuropathy like CIPN
30 induced by various drugs, such as, but is not limited to taxanes, vinca alkaloids and proteasome inhibitors. In some embodiments, the disease or condition is caused by axonal degeneration or neuronal cell damage.

[00225] In a further aspect of this disclosure, a compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt as described herein, including a compound of Formulae 1, 2, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2L, 2m, 3, 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3L, 4, 5, 6, 7, 7a, 7b, 8, 8a, 9, 9a, 10, 11, 12, 13, 13a, 13b, 14, 14a, 14b, 14c, 14d, 14e, 14f, 14g, 14h-1, 14h-2, 14i, 14j, 15, 15a, 16-1, 16-2, 16-1a, 16-2a, 17, 17a, 18, 18a, 19, 20, 21, 21a, 21b, 22, 22a, 23, 23a, 24, 25, 26, 27, 28-1, 28-2, 29-1, 29-2, 29-3, 30-1, 30-2, 30-3, 30-4, 30-5, 31-1, 31-2, 32-1, 32-2, 32-3, 32-4, 32-5, 33-1, 33-2, 33-3, 34-1, 34-2, 34-3, 34-4, 34-5, 34-6, 35-1, 35-2, 35-3, 35-4, 36-1, 36-2, 36-3, 37-1, 37-2, 37-3, 37-4, 37-5, 37-6, 38-1, 38-2, 38-3, 39-1, 39-2, 39-3, 39-4, 40-1, 40-2, 40-3, 41-1, 41-2, 41-3, 41-4, 41-5, 42-1, 42-2, 42-3, 43-1, 43-2, 43-3, 43-4, 44-1, 44-2, 44-3, 44-4, 44-5, 44-6, 44-7, 44-8, 44-9, 44-10, 44-11, 44-12, 44-13, 44-14, 45-1, 45-2, 46-1, 46-2, and 46-3 (e.g., Compounds 1 to 391), and Compounds 1A to 121A disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the compound, tautomer, solvate, stereoisomer, and pharmaceutically acceptable salt, is for use in treating a disease or condition that includes, but is not limited to, amyotrophic lateral sclerosis (ALS), Parkinson's disease, Parkinsonian syndromes, ischemia, stroke, herpes infection, a demyelinating disease such as multiple sclerosis, traumatic brain injury, sepsis, a chronic disease of PNS including inherited neuropathies, such as, but is not limited to Charcot-Marie-Tooth disease and chronic inflammatory demyelinating polyneuropathy (CIDP), an optic nerve disorder such as glaucoma, and retinal ganglion degeneration, colitis, a metabolic disease or disorder such as diabetic neuropathy, nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) and a peripheral neuropathy like CIPN induced by various drugs, such as, but is not limited to taxanes, vinca alkaloids and proteasome inhibitors. In some embodiments, the disease or condition is caused by axonal degeneration or neuronal cell damage.

[00226] Another aspect of the disclosure provides a method of inhibiting or preventing axonal degeneration, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of Formulae 1, 2, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2L, 2m, 3, 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3L, 4, 5, 6, 7, 7a, 7b, 8, 8a, 9, 9a, 10, 11, 12, 13, 13a, 13b, 14, 14a, 14b, 14c, 14d, 14e, 14f, 14g, 14h-1, 14h-2, 14i, 14j, 15, 15a, 16-1, 16-2, 16-1a, 16-2a, 17, 17a, 18, 18a, 19, 20, 21, 21a, 21b, 22, 22a, 23, 23a, 24, 25, 26, 27,

28-1, 28-2, 29-1, 29-2, 29-3, 30-1, 30-2, 30-3, 30-4, 30-5, 31-1, 31-2, 32-1, 32-2, 32-3, 32-4, 32-5, 33-1, 33-2, 33-3, 34-1, 34-2, 34-3, 34-4, 34-5, 34-6, 35-1, 35-2, 35-3, 35-4, 36-1, 36-2, 36-3, 37-1, 37-2, 37-3, 37-4, 37-5, 37-6, 38-1, 38-2, 38-3, 39-1, 39-2, 39-3, 39-4, 40-1, 40-2, 40-3, 41-1, 41-2, 41-3, 41-4, 41-5, 42-1, 42-2, 42-3, 43-1, 43-2, 43-3, 43-4, 44-1, 44-2, 44-3, 44-4, 44-5, 44-6, 44-7, 44-8, 44-9, 44-10, 44-11, 44-12, 44-13, 44-14, 45-1, 45-2, 46-1, 46-2, and 46-3 (e.g., Compounds 1 to 391), and Compounds 1A to 121A disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the compound, tautomer, solvate, stereoisomer, and pharmaceutically acceptable salt.

10 [00227] In another aspect, disclosed herein is use of a compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt as described herein, including a compound of Formulae 1, 2, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2L, 2m, 3, 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3L, 4, 5, 6, 7, 7a, 7b, 8, 8a, 9, 9a, 10, 11, 12, 13, 13a, 13b, 14, 14a, 14b, 14c, 14d, 14e, 14f, 14g, 14h-1, 14h-2, 14i, 14j, 15, 15a, 16-1, 16-2, 16-1a, 16-2a, 17, 17a, 18, 15 18a, 19, 20, 21, 21a, 21b, 22, 22a, 23, 23a, 24, 25, 26, 27, 28-1, 28-2, 29-1, 29-2, 29-3, 30-1, 30-2, 30-3, 30-4, 30-5, 31-1, 31-2, 32-1, 32-2, 32-3, 32-4, 32-5, 33-1, 33-2, 33-3, 34-1, 34-2, 34-3, 34-4, 34-5, 34-6, 35-1, 35-2, 35-3, 35-4, 36-1, 36-2, 36-3, 37-1, 37-2, 37-3, 37-4, 37-5, 37-6, 38-1, 38-2, 38-3, 39-1, 39-2, 39-3, 39-4, 40-1, 40-2, 40-3, 41-1, 41-2, 41-3, 41-4, 41-5, 42-1, 42-2, 42-3, 43-1, 43-2, 43-3, 43-4, 44-1, 44-2, 44-3, 44-4, 44-5, 44-6, 44-7, 44-8, 44-9, 44-10, 44-11, 44-12, 44-13, 44-14, 45-1, 45-2, 46-1, 46-2, and 46-3 (e.g., Compounds 1 to 391), and 20 Compounds 1A to 121A disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the compound, tautomer, solvate, stereoisomer, and pharmaceutically acceptable salt, for the manufacture of a medicament 25 for inhibiting or preventing axonal degeneration or neuronal cells damage.

[00228] In a further aspect of this disclosure, a compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt as described herein, including a compound of Formulae 1, 2, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2L, 2m, 3, 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3L, 4, 5, 6, 7, 7a, 7b, 8, 8a, 9, 9a, 10, 11, 12, 13, 13a, 13b, 14, 14a, 14b, 30 14c, 14d, 14e, 14f, 14g, 14h-1, 14h-2, 14i, 14j, 15, 15a, 16-1, 16-2, 16-1a, 16-2a, 17, 17a, 18, 18a, 19, 20, 21, 21a, 21b, 22, 22a, 23, 23a, 24, 25, 26, 27, 28-1, 28-2, 29-1, 29-2, 29-3, 30-1, 30-2, 30-3, 30-4, 30-5, 31-1, 31-2, 32-1, 32-2, 32-3, 32-4, 32-5, 33-1, 33-2, 33-3, 34-1, 34-2, 34-3,

- 34-4, 34-5, 34-6, 35-1, 35-2, 35-3, 35-4, 36-1, 36-2, 36-3, 37-1, 37-2, 37-3, 37-4, 37-5, 37-6, 38-1, 38-2, 38-3, 39-1, 39-2, 39-3, 39-4, 40-1, 40-2, 40-3, 41-1, 41-2, 41-3, 41-4, 41-5, 42-1, 42-2, 42-3, 43-1, 43-2, 43-3, 43-4, 44-1, 44-2, 44-3, 44-4, 44-5, 44-6, 44-7, 44-8, 44-9, 44-10, 44-11, 44-12, 44-13, 44-14, 45-1, 45-2, 46-1, 46-2, and 46-3 (e.g., Compounds 1 to 391), and
- 5 Compounds 1A to 121A disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the compound, tautomer, solvate, stereoisomer, and pharmaceutically acceptable salt, is for use in inhibiting or preventing axonal degeneration or neuronal cells damage.
- 10 [00229] Another aspect of the disclosure provides a method of modulating, e.g., inhibiting, SARM1 in a subject in need thereof, comprising administering to the subject, a therapeutically effective amount of a compound of Formulae 1, 2, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2L, 2m, 3, 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3L, 4, 5, 6, 7, 7a, 7b, 8, 8a, 9, 9a, 10, 11, 12, 13, 13a, 13b, 14, 14a, 14b, 14c, 14d, 14e, 14f, 14g, 14h-1, 14h-2, 14i, 14j, 15, 15a,
- 15 16-1, 16-2, 16-1a, 16-2a, 17, 17a, 18, 18a, 19, 20, 21, 21a, 21b, 22, 22a, 23, 23a, 24, 25, 26, 27, 28-1, 28-2, 29-1, 29-2, 29-3, 30-1, 30-2, 30-3, 30-4, 30-5, 31-1, 31-2, 32-1, 32-2, 32-3, 32-4, 32-5, 33-1, 33-2, 33-3, 34-1, 34-2, 34-3, 34-4, 34-5, 34-6, 35-1, 35-2, 35-3, 35-4, 36-1, 36-2, 36-3, 37-1, 37-2, 37-3, 37-4, 37-5, 37-6, 38-1, 38-2, 38-3, 39-1, 39-2, 39-3, 39-4, 40-1, 40-2, 40-3, 41-1, 41-2, 41-3, 41-4, 41-5, 42-1, 42-2, 42-3, 43-1, 43-2, 43-3, 43-4, 44-1, 44-2, 44-3, 44-4, 44-
- 20 5, 44-6, 44-7, 44-8, 44-9, 44-10, 44-11, 44-12, 44-13, 44-14, 45-1, 45-2, 46-1, 46-2, and 46-3 (e.g., Compounds 1 to 391), and Compounds 1A to 121A disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the compound, tautomer, solvate, stereoisomer, and pharmaceutically acceptable salt.
- 25 [00230] In another aspect, disclosed herein is use of a compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt as described herein, including a compound of Formulae 1, 2, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2L, 2m, 3, 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3L, 4, 5, 6, 7, 7a, 7b, 8, 8a, 9, 9a, 10, 11, 12, 13, 13a, 13b, 14, 14a, 14b, 14c, 14d, 14e, 14f, 14g, 14h-1, 14h-2, 14i, 14j, 15, 15a, 16-1, 16-2, 16-1a, 16-2a, 17, 17a, 18,
- 30 18a, 19, 20, 21, 21a, 21b, 22, 22a, 23, 23a, 24, 25, 26, 27, 28-1, 28-2, 29-1, 29-2, 29-3, 30-1, 30-2, 30-3, 30-4, 30-5, 31-1, 31-2, 32-1, 32-2, 32-3, 32-4, 32-5, 33-1, 33-2, 33-3, 34-1, 34-2, 34-3, 34-4, 34-5, 34-6, 35-1, 35-2, 35-3, 35-4, 36-1, 36-2, 36-3, 37-1, 37-2, 37-3, 37-4, 37-5, 37-6, 38-

1, 38-2, 38-3, 39-1, 39-2, 39-3, 39-4, 40-1, 40-2, 40-3, 41-1, 41-2, 41-3, 41-4, 41-5, 42-1, 42-2, 42-3, 43-1, 43-2, 43-3, 43-4, 44-1, 44-2, 44-3, 44-4, 44-5, 44-6, 44-7, 44-8, 44-9, 44-10, 44-11, 44-12, 44-13, 44-14, 45-1, 45-2, 46-1, 46-2, and 46-3 (e.g., Compounds 1 to 391), and Compounds 1A to 121A disclosed herein, a tautomer thereof, a solvate or stereoisomer of
5 the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the compound, tautomer, solvate, stereoisomer, and pharmaceutically acceptable salt, for modulating, e.g., inhibiting, SARM1 in a subject in need thereof.

[00231] In another aspect of this disclosure, a compound, tautomer, a solvate or
10 stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt as described herein, including a compound of Formulae 1, 2, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2L, 2m, 3, 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3L, 4, 5, 6, 7, 7a, 7b, 8, 8a, 9, 9a, 10, 11, 12, 13, 13a, 13b, 14, 14a, 14b, 14c, 14d, 14e, 14f, 14g, 14h-1, 14h-2, 14i, 14j, 15, 15a, 16-1, 16-2, 16-1a, 16-2a, 17, 17a, 18, 18a, 19, 20, 21, 21a, 21b, 22, 22a, 23, 23a, 24, 25, 26, 27, 28-1, 28-
15 2, 29-1, 29-2, 29-3, 30-1, 30-2, 30-3, 30-4, 30-5, 31-1, 31-2, 32-1, 32-2, 32-3, 32-4, 32-5, 33-1, 33-2, 33-3, 34-1, 34-2, 34-3, 34-4, 34-5, 34-6, 35-1, 35-2, 35-3, 35-4, 36-1, 36-2, 36-3, 37-1, 37-2, 37-3, 37-4, 37-5, 37-6, 38-1, 38-2, 38-3, 39-1, 39-2, 39-3, 39-4, 40-1, 40-2, 40-3, 41-1, 41-2, 41-3, 41-4, 41-5, 42-1, 42-2, 42-3, 43-1, 43-2, 43-3, 43-4, 44-1, 44-2, 44-3, 44-4, 44-5, 44-6, 44-7, 44-8, 44-9, 44-10, 44-11, 44-12, 44-13, 44-14, 45-1, 45-2, 46-1, 46-2, and 46-3 (e.g.,
20 Compounds 1 to 391), and Compounds 1A to 121A disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the compound, tautomer, solvate, stereoisomer, and pharmaceutically acceptable salt, is for use in modulating, e.g., inhibiting, SARM1 in a subject in need thereof by contacting the subject
25 with the compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, pharmaceutically acceptable salt, or pharmaceutical composition.

[00232] A compound of Formulae 1, 2, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2L, 2m, 3, 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3L, 4, 5, 6, 7, 7a, 7b, 8, 8a, 9, 9a, 10, 11, 12, 13, 13a, 13b, 14, 14a, 14b, 14c, 14d, 14e, 14f, 14g, 14h-1, 14h-2, 14i, 14j, 15, 15a, 16-1, 16-2, 16-
30 1a, 16-2a, 17, 17a, 18, 18a, 19, 20, 21, 21a, 21b, 22, 22a, 23, 23a, 24, 25, 26, 27, 28-1, 28-2, 29-1, 29-2, 29-3, 30-1, 30-2, 30-3, 30-4, 30-5, 31-1, 31-2, 32-1, 32-2, 32-3, 32-4, 32-5, 33-1, 33-2, 33-3, 34-1, 34-2, 34-3, 34-4, 34-5, 34-6, 35-1, 35-2, 35-3, 35-4, 36-1, 36-2, 36-3, 37-1, 37-2, 37-

3, 37-4, 37-5, 37-6, 38-1, 38-2, 38-3, 39-1, 39-2, 39-3, 39-4, 40-1, 40-2, 40-3, 41-1, 41-2, 41-3, 41-4, 41-5, 42-1, 42-2, 42-3, 43-1, 43-2, 43-3, 43-4, 44-1, 44-2, 44-3, 44-4, 44-5, 44-6, 44-7, 44-8, 44-9, 44-10, 44-11, 44-12, 44-13, 44-14, 45-1, 45-2, 46-1, 46-2, and 46-3 (e.g., Compounds 1 to 391), and Compounds 1A to 121A disclosed herein, a tautomer thereof, a
5 solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the compound, tautomer, solvate, stereoisomer, and pharmaceutically acceptable salt may be administered once daily, twice daily, or three times daily, for example, for the treatment of a disease or condition, that includes, but is not limited to, amyotrophic lateral sclerosis (ALS),
10 Parkinson's disease, Parkinsonian syndromes, ischemia, stroke, herpes infection, a demyelinating disease such as multiple sclerosis, traumatic brain injury, sepsis, a chronic disease of PNS including inherited neuropathies, such as, but is not limited to Charcot-Marie-Tooth disease and chronic inflammatory demyelinating polyneuropathy (CIDP), an optic nerve disorder such as glaucoma, and retinal ganglion degeneration, colitis, a
15 metabolic disease or disorder such as diabetic neuropathy, nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) and a peripheral neuropathy like CIPN induced by various drugs, such as, but is not limited to taxanes, vinca alkaloids and proteasome inhibitors. In some embodiments, the disease or condition is caused by axonal degeneration or neuronal cells damage.

20 [00233] A compound of Formulae 1, 2, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2L, 2m, 3, 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3L, 4, 5, 6, 7, 7a, 7b, 8, 8a, 9, 9a, 10, 11, 12, 13, 13a, 13b, 14, 14a, 14b, 14c, 14d, 14e, 14f, 14g, 14h-1, 14h-2, 14i, 14j, 15, 15a, 16-1, 16-2, 16-1a, 16-2a, 17, 17a, 18, 18a, 19, 20, 21, 21a, 21b, 22, 22a, 23, 23a, 24, 25, 26, 27, 28-1, 28-2, 29-1, 29-2, 29-3, 30-1, 30-2, 30-3, 30-4, 30-5, 31-1, 31-2, 32-1, 32-2, 32-3, 32-4, 32-5, 33-1, 33-2,
25 33-3, 34-1, 34-2, 34-3, 34-4, 34-5, 34-6, 35-1, 35-2, 35-3, 35-4, 36-1, 36-2, 36-3, 37-1, 37-2, 37-3, 37-4, 37-5, 37-6, 38-1, 38-2, 38-3, 39-1, 39-2, 39-3, 39-4, 40-1, 40-2, 40-3, 41-1, 41-2, 41-3, 41-4, 41-5, 42-1, 42-2, 42-3, 43-1, 43-2, 43-3, 43-4, 44-1, 44-2, 44-3, 44-4, 44-5, 44-6, 44-7, 44-8, 44-9, 44-10, 44-11, 44-12, 44-13, 44-14, 45-1, 45-2, 46-1, 46-2, and 46-3 (e.g., Compounds 1 to 391), and Compounds 1A to 121A disclosed herein, a tautomer thereof, a
30 solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the compound, tautomer, solvate, stereoisomer, and pharmaceutically acceptable salt may be administered,

for example, various manners, such as orally, topically, rectally, parenterally, by inhalation spray, or via an implanted reservoir, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The term "parenteral" as used herein includes subcutaneous, 5 intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques. The compositions disclosed herein may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art. Parenteral administration can be by continuous infusion over a selected period of time. Other forms of administration contemplated in this disclosure are 10 as described in International Patent Application Nos. WO 2013/075083, WO 2013/075084, WO 2013/078320, WO 2013/120104, WO 2014/124418, WO 2014/151142, and WO 2015/023915.

[00234] The contacting is generally effected by administering to the subject an effective amount of one or more compounds, tautomers, solvates, stereoisomers, and pharmaceutically 15 acceptable salt disclosed herein. Generally, administration is adjusted to achieve a therapeutic dosage of about 0.1 to 50 mg/kg, preferably 0.5 to 10 mg/kg, more preferably 1 to 10 mg/kg, though optimal dosages are compound specific, and generally empirically determined for each compound.

[00235] The dosage administered will be dependent on factors, such as the age, health 20 and weight of the recipient, the extent of disease, type of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired. In general, a daily dosage of the active ingredient can vary, for example, from 0.1 to 2000 milligrams per day. For example, 10-500 milligrams once or multiple times per day may be effective to obtain the desired results.

[00236] In some embodiments, 2 mg to 1500 mg or 5 mg to 1000 mg of a 25 compound of Formulae 1, 2, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2L, 2m, 3, 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3L, 4, 5, 6, 7, 7a, 7b, 8, 8a, 9, 9a, 10, 11, 12, 13, 13a, 13b, 14, 14a, 14b, 14c, 14d, 14e, 14f, 14g, 14h-1, 14h-2, 14i, 14j, 15, 15a, 16-1, 16-2, 16-1a, 16-2a, 17, 17a, 18, 18a, 19, 20, 21, 21a, 21b, 22, 22a, 23, 23a, 24, 25, 26, 27, 28-1, 28-2, 29-1, 29-2, 29-3, 30-1, 30-2, 30-3, 30-4, 30-5, 31-1, 31-2, 32-1, 32-2, 32-3, 32-4, 32-5, 33-1, 33-2, 33-3, 34-1, 34-2, 34-3, 30 34-4, 34-5, 34-6, 35-1, 35-2, 35-3, 35-4, 36-1, 36-2, 36-3, 37-1, 37-2, 37-3, 37-4, 37-5, 37-6, 38-1, 38-2, 38-3, 39-1, 39-2, 39-3, 39-4, 40-1, 40-2, 40-3, 41-1, 41-2, 41-3, 41-4, 41-5, 42-1, 42-2, 42-3, 43-1, 43-2, 43-3, 43-4, 44-1, 44-2, 44-3, 44-4, 44-5, 44-6, 44-7, 44-8, 44-9, 44-10, 44-

11, 44-12, 44-13, 44-14, 45-1, 45-2, 46-1, 46-2, and 46-3 (e.g., Compounds 1 to 391), and Compounds 1A to 121A disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the compound, tautomer, solvate, stereoisomer, and pharmaceutically acceptable salt are administered once daily, twice daily, or three times daily. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein is administered for morning/daytime dosing, with off period at night.

A. Examples

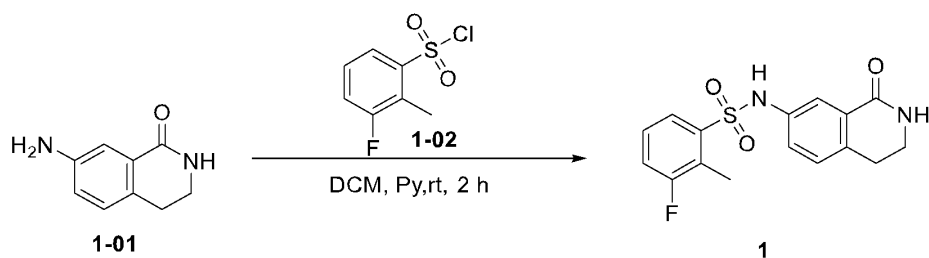
10 [00237] In order that the disclosure described herein may be more fully understood, the following examples are disclosed herein. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this disclosure in any way.

Example I. Synthesis of Exemplary Compounds

15 [00238] The compounds of the disclosure, selected from a compound of the Formulae depicted herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, can be made according to standard chemical practices or as illustrated herein, including the following general synthetic procedures and specific synthetic schemes for Compounds 1 to 354 and Compound 1A to 15A as representative examples of Formula 1.

Preparation of

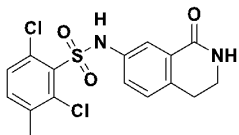
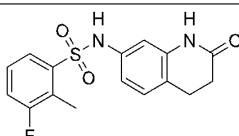
(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((6-fluoropyridin-3-yl)oxy)azetidine-1-yl)methanone (1) Method 1

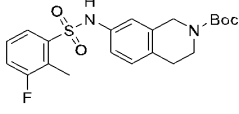
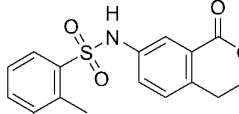
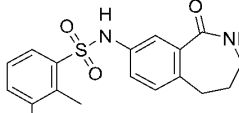


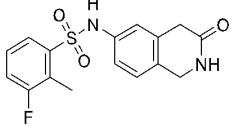
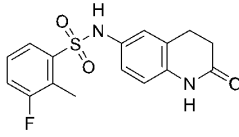
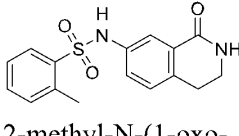
25 To a solution of 7-amino-3,4-dihydroisoquinolin-1(2H)-one **1-01** (150 mg, 0.92 mmol) in DCM (10 mL) was added 3-fluoro-2-methylbenzenesulfonyl chloride **1-02** (192 mg, 0.92 mmol), Pyridine (219 mg, 2.7 mmol). The mixture was stirred at 25 °C for 2 hours. Water was

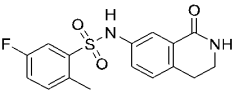
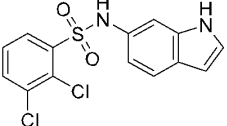
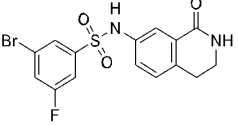
added and the resulting mixture was extracted with EtOAc, dried over Na₂SO₄, and concentrated in vacuo. Purification by silica gel chromatography gave Compound **1** (90 mg, 27.6%) as a white solid. Mass (m/z): 335.40 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.68 (s, 1H), 7.90 (d, *J* = 3.0 Hz, 1H), 7.70 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.57 (d, *J* = 2.0 Hz, 1H), 7.49 – 7.34 (m, 2H), 7.16 (d, *J* = 2.0 Hz, 2H), 3.28 (td, *J* = 6.4, 2.8 Hz, 2H), 2.76 (t, *J* = 6.4 Hz, 2H), 2.48 (d, *J* = 2.4 Hz, 3H).

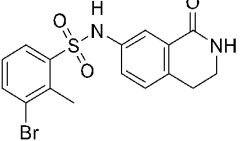
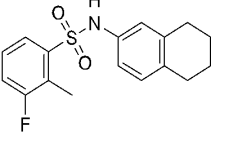
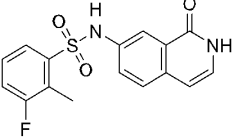
Examples (Compounds) **2-91**, **191**, **196-197**, **204**, and **206**, **208-209**, **211-212**, **217**, **219**, **220**, **224-225**, **227**, **251**, **265-265**, **268-270**, **270A**, **274**, **283**, **298**, **304**, **304A** and **304B** were synthesized using a method like that used in Example 1.

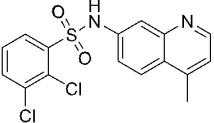
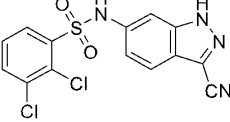
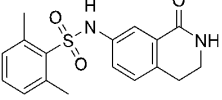
Example No. (Compound No.) Method	Structure and Name	Appearance and Yield	¹ H NMR Data	MS (m/z) [M+H] ⁺
Example 2 Method 1	 2,6-dichloro-3-methyl-N-(1-oxo-3,4-dihydro-2H-isoquinolin-7-yl)benzenesulfonamide	red solid, yield: 30.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.85 (s, 1H), 7.91 (s, 1H), 7.61 (d, <i>J</i> = 2.3 Hz, 1H), 7.59 – 7.49 (m, 2H), 7.25 – 7.15 (m, 2H), 3.31 – 3.25 (m, 2H), 2.76 (t, <i>J</i> = 6.6 Hz, 2H), 2.34 (s, 3H).	385.26
Example 3 Method 1	 3-fluoro-2-methyl-N-(2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)benzenesulfonamide	White solid, yield: 41.7%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.46 (s, 1H), 10.01 (s, 1H), 7.72 (dd, <i>J</i> = 7.6, 1.6 Hz, 1H), 7.41 (m, 2H), 6.97 (d, <i>J</i> = 8.4 Hz, 1H), 6.68 (d, <i>J</i> = 2.0 Hz, 1H), 6.58 (dd, <i>J</i> = 8.0, 2.4 Hz, 1H), 2.72 (t, <i>J</i> = 7.2 Hz, 2H), 2.48 (d, <i>J</i> = 2.4 Hz, 3H), 2.36 (t, <i>J</i> = 8.4 Hz, 2H).	335.17

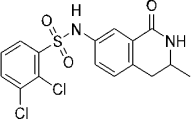
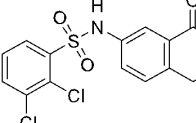
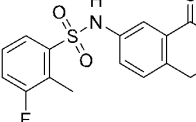
Example 4 Method 1	 (tert-butyl 7-((3-fluoro-2-methylphenyl)sulfonamido)-3,4-dihydroisoquinoline-2(1H)-carboxylate	White solid, yield: 19.8%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.46 (s, 1H), 7.73 (d, <i>J</i> = 6.8, 1H), 7.47-7.37 (m, 2H), 7.01 (d, <i>J</i> = 8.4 Hz, 1H), 6.89 – 6.83 (m, 2H), 4.35 (s, 2H), 3.47 (t, <i>J</i> = 5.6 Hz, 2H), 2.63 (t, <i>J</i> = 6.0, 2H), 2.48 (d, <i>J</i> = 2.4 Hz, 3H), 1.40 (s, 9H).	420.5
Example 5 Method 1	 3-fluoro-2-methyl-N-(1-oxoisochroman-7-yl)benzenesulfonamide	White solid, yield: 5.0%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.95 (s, 1H), 7.73 – 7.71 (m, 1H), 7.59 (d, <i>J</i> = 2.4 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.29 – 7.23 (m, 2H), 4.41 (t, <i>J</i> = 6.0 Hz, 2H), 2.91 (t, <i>J</i> = 6.0 Hz, 2H), 2.48 (s, 3H).	336.1
Example 6 Method 1	 3-fluoro-2-methyl-N-(1-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yl)benzenesulfonamide	White solid, yield: 30.3%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.64 (s, 1H), 8.01 (t, <i>J</i> = 5.6 Hz, 1H), 7.71 (dd, <i>J</i> = 7.6, 1.6 Hz, 1H), 7.47-7.37 (m, 2H), 7.20 (t, <i>J</i> = 1.6 Hz, 1H), 7.10 (d, <i>J</i> = 1.6 Hz, 2H), 2.81 (q, <i>J</i> = 6.4 Hz, 2H), 2.61 (t, <i>J</i> = 6.8 Hz, 2H), 2.47 (d, <i>J</i> = 2.4 Hz, 3H), 1.79 (p, <i>J</i> = 6.8 Hz, 2H).	349.2

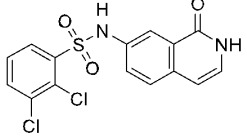
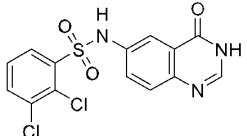
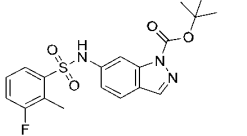
Example 7 Method 1	 3-fluoro-2-methyl-N-(3-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)benzenesulfonamide	White solid, yield: 19.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.80 (s, 1H), 7.91 (s, 1H), 7.73 (dd, <i>J</i> = 7.2, 2.0 Hz, 1H), 7.41 – 7.33 (m, 2H), 7.06 (d, <i>J</i> = 8.0 Hz, 1H), 6.88 – 6.84 (m, 2H), 4.19 (s, 2H), 3.29 (s, 2H), 2.47 (d, <i>J</i> = 2.4 Hz, 3H).	335.1
Example 8 Method 1	 3-fluoro-2-methyl-N-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)benzenesulfonamide	White solid, yield: 41.9%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.22 (s, 1H), 9.97 (s, 1H), 7.67 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.47 – 7.35 (m, 2H), 6.87 (d, <i>J</i> = 2.4 Hz, 1H), 6.83 (dd, <i>J</i> = 8.4, 2.4 Hz, 1H), 6.69 (d, <i>J</i> = 8.4 Hz, 1H), 2.77 (dd, <i>J</i> = 8.8, 6.8 Hz, 2H), 2.47 (d, <i>J</i> = 2.0 Hz, 3H), 2.38 (dd, <i>J</i> = 8.4, 6.8 Hz, 2H).	335.1
Example 9 Method 1	 2-methyl-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 6.49%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.46 (s, 1H), 7.89 (s, 1H), 7.85 (d, <i>J</i> = 8.4 Hz, 1H), 7.57 (d, <i>J</i> = 2.0 Hz, 1H), 7.51 (td, <i>J</i> = 7.6, 1.2 Hz, 1H), 7.37 – 7.33 (m, 2H), 7.19 – 7.13 (m, 2H), 3.28 (td, <i>J</i> = 6.4, 2.8 Hz, 2H), 2.75 (t, <i>J</i> = 6.4 Hz, 2H), 2.59 (s, 3H).	316.3

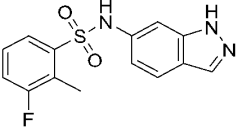
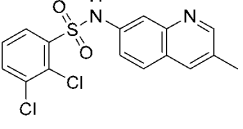
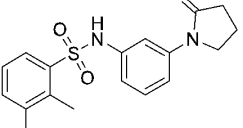
Example 10 Method 1	 5-fluoro-2-methyl-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 6.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.59 (s, 1H), 7.91 (t, <i>J</i> = 2.8 Hz, 1H), 7.61 (dd, <i>J</i> = 2.8, 8.8 Hz, 1H), 7.56 (d, <i>J</i> = 1.6 Hz, 1H), 7.45 – 7.36 (m, 1H), 7.21 – 7.16 (m, 1H), 3.30 (td, <i>J</i> = 2.8, 6.4 Hz, 2H), 2.77 (t, <i>J</i> = 6.8 Hz, 2H), 2.54 (s, 3H).	334.3
Example 11 Method 1	 2,3-dichloro-N-(1H-indol-6-yl)benzenesulfonamide	white solid, yield: 23.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.01 (s, 1H), 10.44 (s, 1H), 7.91 (dd, <i>J</i> = 8.0, 1.5 Hz, 1H), 7.85 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.45 (t, <i>J</i> = 8.0 Hz, 1H), 7.37 (d, <i>J</i> = 8.4 Hz, 1H), 7.25 (t, <i>J</i> = 2.8 Hz, 1H), 7.20 – 7.14 (m, 1H), 6.80 (dd, <i>J</i> = 8.4, 2.0 Hz, 1H), 6.31 – 6.30 (m, 1H).	340.0
Example 12 Method 1	 3-bromo-5-fluoro-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 8.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.54 (s, 1H), 7.93 (t, <i>J</i> = 2.8 Hz, 1H), 7.90 (td, <i>J</i> = 2.0, 8.4 Hz, 1H), 7.71 (t, <i>J</i> = 1.6 Hz, 1H), 7.56 – 7.53 (m, 2H), 7.21 (d, <i>J</i> = 1.6 Hz, 2H), 3.29 (m, 2H), 2.80 (t, <i>J</i> = 6.8 Hz, 2H).	399.2

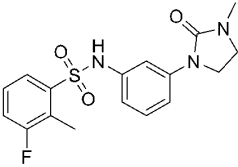
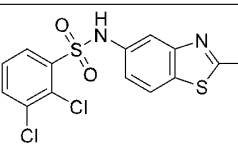
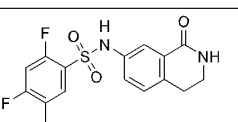
Example 13 Method 1	 3-bromo-2-methyl-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 10.9%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.67 (s, 1H), 7.91 – 7.86 (m, 3H), 7.57 (t, <i>J</i> = 1.6 Hz, 1H), 7.31 (t, <i>J</i> = 8.0 Hz, 1H), 7.17 (d, <i>J</i> = 1.6 Hz, 2H), 3.30 (dt, <i>J</i> = 2.8, 6.4 Hz, 2H), 2.77 (t, <i>J</i> = 6.4 Hz, 2H), 2.67 (s, 3H).	396.1
Example 14 Method 1	 3-fluoro-2-methyl-N-(5,6,7,8-tetrahydronaphthalen-2-yl)benzenesulfonamide	White solid, yield: 36.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.30 (s, 1H), 7.71 (dd, <i>J</i> = 7.6, 1.6 Hz, 1H), 7.46 – 7.36 (m, 2H), 6.89 (d, <i>J</i> = 8.0 Hz, 1H), 6.79 – 6.74 (m, 2H), 2.57 (p, <i>J</i> = 3.2 Hz, 4H), 2.47 (d, <i>J</i> = 2.4 Hz, 3H), 1.64 (p, <i>J</i> = 3.2 Hz, 4H).	320.1
Example 15 Method 1	 3-fluoro-2-methyl-N-(1-oxo-1,2-dihydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 48.2%	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 9.72 (s, 1H), 8.22-8.06 (m, 2H), 7.84 (d, <i>J</i> = 7.2 Hz, 1H), 7.68 (d, <i>J</i> = 8.4 Hz, 1H), 7.52 – 7.48 (m, 1H), 7.32 – 7.17 (m, 2H), 7.07 (s, 1H), 6.54 (s, 1H), 2.57 (d, <i>J</i> = 2.0 Hz, 3H).	333.2

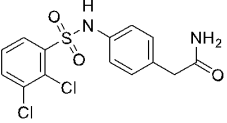
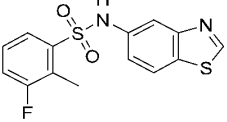
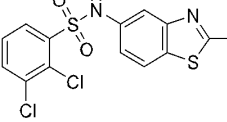
Example 16 Method 1	 2,3-dichloro-N-(4-methylquinolin-7-yl)benzenesulfonamide	White solid, yield: 42.3%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.29 (s, 1H), 8.64 (d, <i>J</i> = 4.4 Hz, 1H), 8.16 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 8.01 (d, <i>J</i> = 9.0 Hz, 1H), 7.91 (dd, <i>J</i> = 8.2, 1.6 Hz, 1H), 7.62 (d, <i>J</i> = 2.4 Hz, 1H), 7.58 (t, <i>J</i> = 8.0 Hz, 1H), 7.43 (dd, <i>J</i> = 9.0, 2.4 Hz, 1H), 7.27 – 7.19 (m, 1H), 2.59 (s, 3H).	267.1
Example 17 Method 1	 6-nitro-1H-indazole-3-carbonitrile	White solid, yield: 17.1%	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.02 – 8.00 (m, 1H), 7.68 – 7.59 (m, 2H), 7.39 – 7.31 (m, 2H), 7.1 – 7.08 (s, 1H).	368.9
Example 18 Method 1	 2,6-dimethyl-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 24.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.30 (s, 1H), 7.86 (t, <i>J</i> = 2.8 Hz, 1H), 7.53 (d, <i>J</i> = 2.4 Hz, 1H), 7.31 (t, <i>J</i> = 8.0 Hz, 1H), 7.18 – 7.07 (m, 3H), 7.09 (dd, <i>J</i> = 8.0, 2.4 Hz, 1H), 3.3 (td, <i>J</i> = 6.4, 2.8 Hz, 2H), 2.74 (t, <i>J</i> = 6.4 Hz, 2H), 2.60 (s, 6H).	331.2

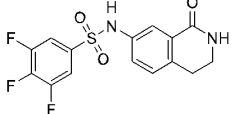
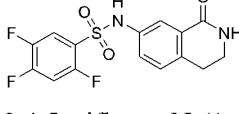
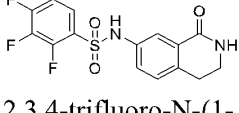
Example 19 Method 1	 2,3-dichloro-N-(3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 18.8%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.87 (s, 1H), 8.05 – 7.98 (m, 1H), 7.95 – 7.89 (m, 2H), 7.63 – 7.50 (m, 2H), 7.18 (d, <i>J</i> = 9.4 Hz, 1H), 3.31 – 3.27 (m, 1H), 3.17 (d, <i>J</i> = 5.2 Hz, 3H), 1.13 (d, <i>J</i> = 6.4 Hz, 3H).	384.98
Example 20 Method 1	 2,3-dichloro-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 46.0%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.84 (s, 1H), 8.02 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.93 – 7.91 (m, 2H), 7.61 (d, <i>J</i> = 2.0 Hz, 1H), 7.54 (t, <i>J</i> = 8.0 Hz, 1H), 7.22 – 7.17 (m, 2H), 3.31 (dd, <i>J</i> = 6.4, 2.8 Hz, 2H), 2.77 (t, <i>J</i> = 6.4 Hz, 2H).	371.1
Example 21 Method 1	 3-fluoro-2-methyl-N-(2-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 10.9%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.78 (s, 1H), 7.71 (dd, <i>J</i> = 1.6, 7.6 Hz, 1H), 7.56 (d, <i>J</i> = 2.4 Hz, 1H), 7.43 – 7.34 (m, 2H), 7.14 – 7.09 (m, 2H), 3.45 (t, <i>J</i> = 6.8 Hz, 2H), 2.97 (s, 3H), 2.83 (t, <i>J</i> = 6.4 Hz, 2H), 2.48 (d, <i>J</i> = 2.4 Hz, 3H).	349.1

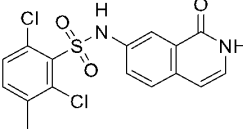
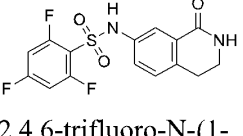
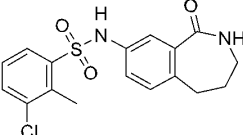
Example 22 Method 1	 2,3-dichloro-N-(1-oxo-1,2-dihydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 37.3%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.19 (d, <i>J</i> = 5.6 Hz, 1H), 11.12 (s, 1H), 8.05 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.89 – 7.87 (m, 2H), 7.53 (t, <i>J</i> = 8.0 Hz, 2H), 7.46 (dd, <i>J</i> = 8.8, 2.4 Hz, 1H), 7.06 (dd, <i>J</i> = 5.6, 6.8 Hz, 1H), 6.43 (d, <i>J</i> = 6.8 Hz, 1H).	368.8
Example 23 Method 1	 2,3-dichloro-N-(4-oxo-3,4-dihydroquinazolin-6-yl)benzenesulfonamide	White solid, yield: 1.4%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.74 (s, 1H), 8.30 (s, 1H), 7.93 (dd, <i>J</i> = 7.6, 1.6 Hz, 1H), 7.74 (s, 1H), 7.64 (d, <i>J</i> = 8.0 Hz, 1H), 7.50 (d, <i>J</i> = 2.4 Hz, 1H), 7.37 – 7.24 (m, 3H).	370.1
Example 24 Method 1	 tert-butyl 6-((3-fluoro-2-methylphenyl)sulfonamido)-1H-indazole-1-carboxylate	White solid, yield: 12.3%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.99 (s, 1H), 8.27 (s, 1H), 7.87 – 7.82 (s, 1H), 7.75 (m, 2H), 7.42 – 7.37 (m, 2H), 7.14 (dd, <i>J</i> = 8.8, 2.0 Hz, 1H), 2.49 (m, 3H), 1.62 (s, 9H).	406.2

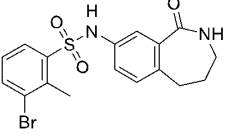
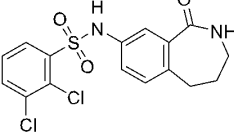
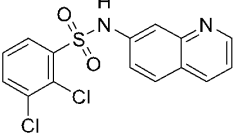
Example 25 Method 1	 3-fluoro-N-(1H-indazol-6-yl)-2-methylbenzenesulfonamide	white solid, yield: 33.3%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.83 (s, 1H), 10.65 (s, 1H), 7.94 (d, <i>J</i> = 1.2 Hz, 1H), 7.73 (dd, <i>J</i> = 7.6, 1.6 Hz, 1H), 7.62 (d, <i>J</i> = 8.4 Hz, 1H), 7.44 – 7.37 (m, 2H), 7.25 (d, <i>J</i> = 1.2 Hz, 1H), 6.89 (dd, <i>J</i> = 8.4, 1.6 Hz, 1H), 2.49 (m, 3H).	306.2
Example 26 Method 1	 2,3-dichloro-N-(3-methylquinolin-7-yl)benzenesulfonamide	Light yellow solid, yield: 38%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.65 (d, <i>J</i> = 2.2 Hz, 1H), 8.14 (dd, <i>J</i> = 7.9, 1.5 Hz, 1H), 7.98 (s, 1H), 7.90 (dd, <i>J</i> = 8.1, 1.5 Hz, 1H), 7.77 (d, <i>J</i> = 8.9 Hz, 1H), 7.66 – 7.53 (m, 2H), 7.36 (dd, <i>J</i> = 8.8, 2.2 Hz, 1H), 2.40 (s, 3H).	376.02
Example 27 Method 1	 3-fluoro-2-methyl-N-(3-(2-oxopyrrolidin-1-yl)phenyl)benzenesulfonamide	orange solid, yield: 5.0%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.57 (br s, 1H), 7.76 (d, <i>J</i> = 7.2 Hz, 1H), 7.56 (s, 1H), 7.44-7.38 (m, 2H), 7.18 (d, <i>J</i> = 5.2 Hz, 2H), 6.82-6.79 (m, 1H), 3.70 (t, <i>J</i> = 7.2 Hz, 2H), 2.47-2.44 (m, 5H), 2.05-1.99 (m, 2H).	349.0

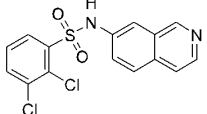
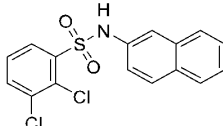
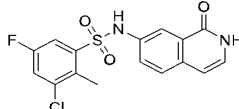
Example 28 Method 1	 3-fluoro-2-methyl-N-(3-(3-methyl-2-oxoimidazolidin-1-yl)phenyl)benzenesulfonamide	Light yellow solid, yield: 33.4%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.49 (s, 1H), 7.76 (d, <i>J</i> = 7.2 Hz, 1H), 7.48-7.40 (m, 3H), 7.13-7.11 (m, 2H), 6.69-6.67 (m, 1H), 3.67-3.63 (m, 2H), 3.41-3.37 (m, 2H), 2.74 (s, 3H), 2.51 (s, 3H).	364.0
Example 29 Method 1	 2,3-dichloro-N-(2-methylbenzo[d]thiazol-5-yl)benzenesulfonamide	White solid, yield: 32.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.98 (s, 1H), 8.06 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.94 – 7.84 (m, 2H), 7.58 (d, <i>J</i> = 2.0 Hz, 1H), 7.53 (t, <i>J</i> = 8.0 Hz, 1H), 7.16 (dd, <i>J</i> = 8.6, 2.2 Hz, 1H), 2.73 (s, 3H).	373.2
Example 30 Method 1	 2,4-difluoro-5-methyl-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 16.6%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.63 (s, 1H), 7.90 (s, 1H), 7.77 (t, <i>J</i> = 8.4 Hz, 1H), 7.59 (d, <i>J</i> = 2.4 Hz, 1H), 7.45 (t, <i>J</i> = 10.0 Hz, 1H), 7.24 – 7.16 (m, 2H), 3.29 – 3.26 (m, 2H), 2.78 (t, <i>J</i> = 6.6 Hz, 2H), 2.22 (s, 3H).	353.3

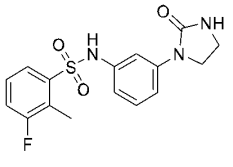
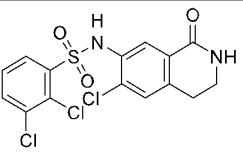
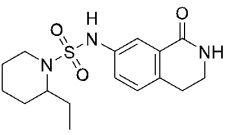
Example 31 Method 1	 2-(4-((2,3-dichlorophenyl)sulfonamido)phenyl)acetamide	Light yellow solid, yield: 28.4%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.66 (s, 1H), 8.00 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.90 (d, <i>J</i> = 8.2 Hz, 1H), 7.52 (d, <i>J</i> = 8.0 Hz, 1H), 7.36 (br s, 1H), 7.10 (d, <i>J</i> = 8.6 Hz, 2H), 7.02 (d, <i>J</i> = 8.6 Hz, 2H), 6.79 (br s, 1H), 3.24 (s, 2H).	359.3
Example 32 Method 1	 N-(benzo[d]thiazol-5-yl)-3-fluoro-2-methylbenzenesulfonamide	White solid, yield: 20.3%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.80 (br s, 1H), 9.35 (s, 1H), 8.02 (d, <i>J</i> = 8.6 Hz, 1H), 7.77 (dd, <i>J</i> = 7.4, 1.6 Hz, 1H), 7.72 (d, <i>J</i> = 2.0 Hz, 1H), 7.48 – 7.35 (m, 2H), 7.23 (dd, <i>J</i> = 8.7, 2.2 Hz, 1H), 3.32 (s, 3H).	323.2
Example 33 Method 1	 2,3-dichloro-N-(2-chlorobenzo[d]thiazol-5-yl)benzenesulfonamide	White solid, yield: 26.3%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.13 (s, 1H), 8.09 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.96 (d, <i>J</i> = 8.8 Hz, 1H), 7.91 (dd, <i>J</i> = 8.1, 1.5 Hz, 1H), 7.61 (d, <i>J</i> = 2.1 Hz, 1H), 7.54 (t, <i>J</i> = 8.0 Hz, 1H), 7.25 (dd, <i>J</i> = 8.8, 2.2 Hz, 1H).	393.1

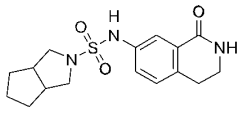
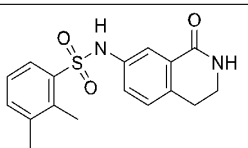
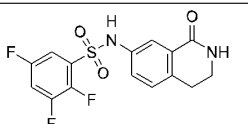
Example 34 Method 1	 3,4,5-trifluoro-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 43.7%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.58 (br s, 1H), 7.96 (s, 1H), 7.69 (t, <i>J</i> = 6.4 Hz, 2H), 7.58 (d, <i>J</i> = 2.0 Hz, 1H), 7.29 – 7.08 (m, 2H), 3.30 (td, <i>J</i> = 6.4, 2.8 Hz, 3H), 2.80 (t, <i>J</i> = 6.4 Hz, 2H).	357.3
Example 35 Method 1	 2,4,5-trifluoro-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 45.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.85 (s, 1H), 7.95 (s, 1H), 7.92 – 7.80 (m, 2H), 7.59 (d, <i>J</i> = 2.0 Hz, 1H), 7.29 – 7.16 (m, 2H), 3.30 (td, <i>J</i> = 6.4, 2.8 Hz, 2H), 2.79 (t, <i>J</i> = 6.4 Hz, 2H).	357.3
Example 36 Method 1	 2,3,4-trifluoro-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 55.0%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.93 (d, <i>J</i> = 2.8 Hz, 1H), 7.72 – 7.61 (m, 1H), 7.58 (d, <i>J</i> = 2.0 Hz, 1H), 7.53 – 7.41 (m, 1H), 7.24 – 7.15 (m, 2H), 3.32 – 3.27 (m, 2H), 2.79 (t, <i>J</i> = 6.4 Hz, 2H).	357.1

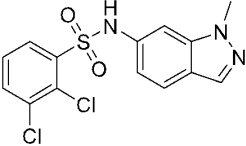
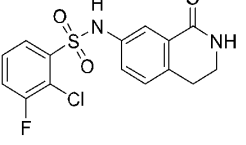
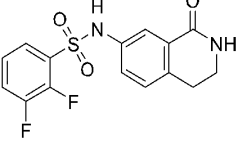
Example 37 Method 1	 2,6-dichloro-3-methyl-N-(1-oxo-2H-isoquinolin-7-yl)benzenesulfonamide	white solid, yield: 20.6%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.17 (s, 1H), 11.05 (s, 1H), 7.89 (d, <i>J</i> = 2.1 Hz, 1H), 7.54 (t, <i>J</i> = 8.7 Hz, 3H), 7.49 – 7.44 (m, 1H), 7.04 (t, 1H), 6.42 (d, <i>J</i> = 7.0 Hz, 1H), 2.33 (s, 3H).	383.25
Example 38 Method 1	 2,4,6-trifluoro-N-(1-oxo-3,4-dihydro-2H-isoquinolin-7-yl)benzenesulfonamide	White solid, yield: 13.4%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.99 (s, 1H), 7.95 (t, <i>J</i> = 2.8 Hz, 1H), 7.65 – 7.62 (m, 1H), 7.46 – 7.39 (m, 2H), 7.23 (d, <i>J</i> = 2.1 Hz, 2H), 3.32 – 3.27 (m, 2H), 2.80 (t, <i>J</i> = 6.6 Hz, 2H).	357.0
Example 39 Method 1	 3-chloro-2-methyl-N-(1-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yl)benzenesulfonamide	White solid, yield: 23.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.67 (s, 1H), 8.03 (t, <i>J</i> = 6.0 Hz, 1H), 7.86 (dd, <i>J</i> = 8.0, 1.2 Hz, 1H), 7.71 (dd, <i>J</i> = 8.0, 1.4 Hz, 1H), 7.39 (t, <i>J</i> = 8.0 Hz, 1H), 7.22 – 7.17 (m, 1H), 7.14 – 7.05 (m, 2H), 2.81 (q, <i>J</i> = 6.4 Hz, 2H), 2.65 – 2.56 (m, 5H), 1.79 (p, <i>J</i> = 6.8 Hz, 2H).	365.1

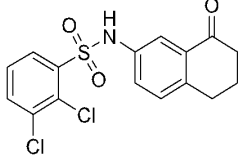
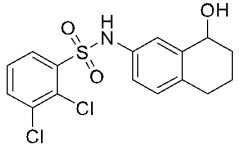
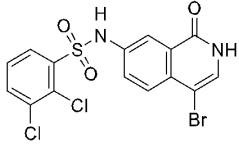
Example 40 Method 1	 3-bromo-2-methyl-N-(1-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yl)benzenesulfonamide	White solid, yield: 20.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.68 (br s, 1H), 8.03 (t, <i>J</i> = 6.0 Hz, 1H), 7.89 (ddd, <i>J</i> = 10.0, 8.0, 1.2 Hz, 2H), 7.31 (t, <i>J</i> = 8.0 Hz, 1H), 7.20 (d, <i>J</i> = 2.0 Hz, 1H), 7.15 – 7.05 (m, 2H), 2.81 (q, <i>J</i> = 6.4 Hz, 2H), 2.66 (s, 3H), 2.61 (t, <i>J</i> = 7.0 Hz, 2H), 1.79 (p, <i>J</i> = 6.8 Hz, 2H).	409.2
Example 41 Method 1	 2,3-dichloro-N-(1-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yl)benzenesulfonamide	White solid, yield: 21.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.86 (s, 1H), 8.06 – 7.98 (m, 2H), 7.92 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.55 (t, <i>J</i> = 8.0 Hz, 1H), 7.24 (t, <i>J</i> = 1.4 Hz, 1H), 7.15 – 7.09 (m, 2H), 2.80 (q, <i>J</i> = 6.4 Hz, 2H), 2.60 (t, <i>J</i> = 7.0 Hz, 2H), 1.79 (p, <i>J</i> = 6.8 Hz, 2H).	385.1
Example 42 Method 1	 2,3-dichloro-N-(quinolin-7-yl)benzenesulfonamide	White solid, yield: 17.8%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.33 (br s, 1H), 8.79 (d, <i>J</i> = 2.6 Hz, 1H), 8.23 (dd, <i>J</i> = 8.2, 1.6 Hz, 1H), 8.17 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.91 (dd, <i>J</i> = 8.2, 1.6 Hz, 1H), 7.88 (d, <i>J</i> = 8.8 Hz, 1H), 7.64 – 7.54 (m, 2H), 7.44 – 7.36 (m, 2H).	353.1

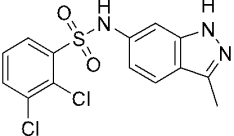
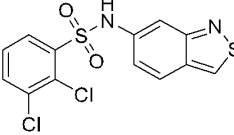
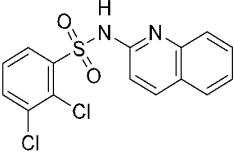
Example 43 Method 1	 2,3-dichloro-N-(isoquinolin-7-yl)benzenesulfonamide	White solid, yield: 22.3%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.30 (br s, 1H), 9.19 (s, 1H), 8.39 (d, <i>J</i> = 5.6 Hz, 1H), 8.15 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.93 – 7.84 (m, 2H), 7.73 (d, <i>J</i> = 2.2 Hz, 1H), 7.71 (d, <i>J</i> = 5.6 Hz, 1H), 7.60 – 7.49 (m, 2H).	353.2
Example 44 Method 1	 2,3-dichloro-N-(naphthalen-2-yl)benzenesulfonamide	White solid, yield: 43.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.03 (br s, 1H), 8.11 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.88 (dd, <i>J</i> = 8.0, 1.4 Hz, 1H), 7.84 – 7.71 (m, 3H), 7.55 (d, <i>J</i> = 2.2 Hz, 1H), 7.52 (t, <i>J</i> = 8.0 Hz, 1H), 7.47 – 7.36 (m, 2H), 7.31 (dd, <i>J</i> = 8.8, 2.2 Hz, 1H).	352.1
Example 45 Method 1	 3-chloro-5-fluoro-2-methyl-N-(1-oxo-1,2-dihydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 16.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.24 (d, <i>J</i> = 5.8 Hz, 1H), 11.03 (s, 1H), 7.85 (d, <i>J</i> = 2.4 Hz, 1H), 7.80 (dd, <i>J</i> = 8.2, 2.8 Hz, 1H), 7.69 (dd, <i>J</i> = 8.4, 2.8 Hz, 1H), 7.58 (d, <i>J</i> = 8.6 Hz, 1H), 7.45 (dd, <i>J</i> = 8.6, 2.4 Hz, 1H), 7.07 (dd, <i>J</i> = 7.1, 5.8 Hz, 1H), 6.46 (d, <i>J</i> = 7.1 Hz, 1H), 2.60 (s, 3H).	367.3

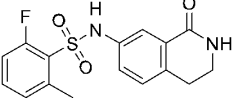
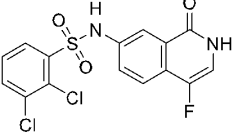
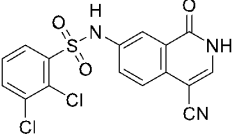
Example 46 Method 1	 3-fluoro-2-methyl-N-(3-(2-oxoimidazolidin-1-yl)phenyl)benzenesulfonamide	White solid, yield: 3.0%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.47 (t, <i>J</i> = 2.4 Hz, 1H), 7.75 (d, <i>J</i> = 7.6 Hz, 1H), 7.36-7.44 (m, 3H), 7.07-7.13 (m, 2H), 6.94 (s, 1H), 6.88-6.68 (m, 1H), 3.71 (d, <i>J</i> = 8.0, 2H) 3.59 (d, <i>J</i> = 8.0, 2H) 2.32-2.47 (m, 3H).	350.1
Example 47 Method 1	 2,3-dichloro-N-(6-chloro-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	light yellow solid. yield: 18.4%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.65 (d, <i>J</i> = 2.2 Hz, 1H), 8.14 (dd, <i>J</i> = 7.9, 1.5 Hz, 1H), 7.98 (s, 1H), 7.90 (dd, <i>J</i> = 8.1, 1.5 Hz, 1H), 7.77 (d, <i>J</i> = 8.9 Hz, 1H), 7.66 – 7.50 (m, 2H), 7.36 (dd, <i>J</i> = 8.8, 2.2 Hz, 1H), 2.40 (s, 3H).	404.97
Example 48 Method 1 Mixture of Stereoisomers	 2-ethyl-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)piperidine-1-sulfonamide	White solid, yield: 3.3%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.86 (s, 1H), 7.88 (s, 1H), 7.60 (d, <i>J</i> = 2.0 Hz, 1H), 7.17 (dd, <i>J</i> = 9.4, 5.2 Hz, 2H), 3.65 (dd, <i>J</i> = 12.0, 7.2 Hz, 1H), 3.41 (dd, <i>J</i> = 13.8, 4.0 Hz, 1H), 3.27 (d, <i>J</i> = 2.8 Hz, 1H), 2.85 – 2.75 (m, 3H), 1.57 – 1.25 (m, 8H), 1.00 (m, 1H), 0.72 (t, <i>J</i> = 7.4 Hz, 3H).	338.0

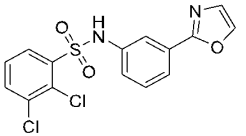
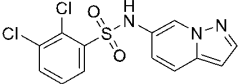
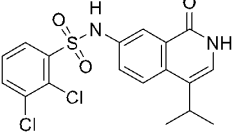
Example 49 Method 1	 N-(1-oxo-3,4-dihydro-2H-isoquinolin-7-yl)-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-2-sulfonamide	White solid, yield: 12.7%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.69 (d, <i>J</i> = 2.3 Hz, 1H), 7.29 – 7.20 (m, 2H), 3.32 (m, 2H), 3.23 (m, 2H), 2.86 – 2.79 (m, 4H), 2.58 – 2.52 (m, 2H), 1.67 – 1.56 (m, 2H), 1.42 – 1.28 (m, 2H), 1.20 – 1.10 (m, 2H).	336.0
Example 50 Method 1	 2,3-dimethyl-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	Light brown solid, yield: 45.8%	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.81 (dd, <i>J</i> = 8.0, 1.4 Hz, 1H), 7.61 (d, <i>J</i> = 2.4 Hz, 1H), 7.35 (d, <i>J</i> = 7.8 Hz, 1H), 7.22 (dd, <i>J</i> = 8.0, 2.4 Hz, 1H), 7.15 (t, <i>J</i> = 7.8 Hz, 1H), 7.11 (d, <i>J</i> = 8.0 Hz, 1H), 3.40 (t, <i>J</i> = 6.4 Hz, 2H), 2.84 (t, <i>J</i> = 6.4 Hz, 2H), 2.56 (s, 3H), 2.30 (s, 3H).	331.1
Example 51 Method 1	 2,3,5-trifluoro-N-(1-oxo-3,4-dihydro-2H-isoquinolin-7-yl)benzenesulfonamide	brown solid, yield: 17.9%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.00 (s, 1H), 7.96 (d, <i>J</i> = 2.8 Hz, 1H), 7.95 – 7.86 (m, 1H), 7.60 (t, <i>J</i> = 1.4 Hz, 1H), 7.50 – 7.40 (m, 1H), 7.23 (d, <i>J</i> = 2.1 Hz, 2H), 3.30 (m, 2H), 2.80 (t, <i>J</i> = 6.6 Hz, 2H).	357.0

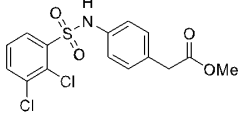
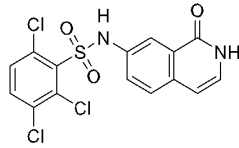
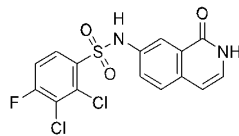
Example 52 Method 1	 2,3-dichloro-N-(1-methyl-1H-indazol-6-yl)benzenesulfonamide	White solid, yield: 65.4%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.99 (br s, 1H), 8.13 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.92 (d, <i>J</i> = 1.0 Hz, 1H), 7.88 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.63 (d, <i>J</i> = 8.4 Hz, 1H), 7.53 (t, <i>J</i> = 8.0 Hz, 1H), 7.24 (s, 1H), 6.93 (dd, <i>J</i> = 8.4, 2.0 Hz, 1H), 3.92 (s, 3H).	356.2
Example 53 Method 1	 2-chloro-3-fluoro-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 35.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.85 (s, 1H), 7.93 (s, 1H), 7.86 (d, <i>J</i> = 6.4 Hz, 1H), 7.70 (td, <i>J</i> = 8.4, 1.6 Hz, 1H), 7.60 (d, <i>J</i> = 2.0 Hz, 1H), 7.59 – 7.52 (m, 1H), 7.24 – 7.10 (m, 2H), 3.28 (td, <i>J</i> = 6.4, 2.8 Hz, 2H), 2.77 (t, <i>J</i> = 6.4 Hz, 2H).	355.2
Example 54 Method 1	 2,3-difluoro-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 32.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.87 (s, 1H), 7.95 (s, 1H), 7.78 – 7.71 (m, 1H), 7.67 – 7.53 (m, 2H), 7.41 – 7.35 (m, 1H), 7.27 – 7.14 (m, 2H), 3.29 (td, <i>J</i> = 6.7, 2.8 Hz, 2H), 2.79 (t, <i>J</i> = 6.6 Hz, 2H).	339.2

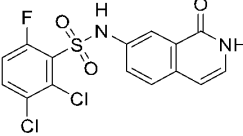
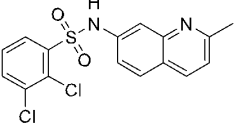
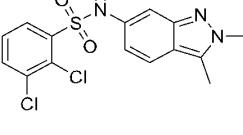
Example 55 Method 2	 2,3-dichloro-N-(8-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)benzenesulfonamide	White solid, yield: 40%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.92 (s, 1H), 8.02 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.92 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.59 (d, <i>J</i> = 2.4 Hz, 1H), 7.55 (t, <i>J</i> = 8.0 Hz, 1H), 7.32 – 7.22 (m, 2H), 2.81 (t, <i>J</i> = 6.0 Hz, 2H), 2.53 (d, <i>J</i> = 5.6 Hz, 2H), 1.95 (p, <i>J</i> = 6.4 Hz, 2H).	370.2
Example 56 Method 1 Mixture of Stereoisomers	 2,3-dichloro-N-(8-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)benzenesulfonamide	White solid, yield: 38.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.59 (s, 1H), 8.00 (dd, <i>J</i> = 8.0, 1.5 Hz, 1H), 7.91 (dd, <i>J</i> = 8.1, 1.5 Hz, 1H), 7.53 (t, <i>J</i> = 8.0 Hz, 1H), 7.19 (d, <i>J</i> = 2.0 Hz, 1H), 6.95 – 6.86 (m, 2H), 5.10 (d, <i>J</i> = 6.2 Hz, 1H), 4.39 (s, 1H), 2.64 – 2.52 (m, 2H), 1.88 – 1.74 (m, 2H), 1.64 – 1.47 (m, 2H).	372.1
Example 57 Method 1	 N-(4-bromo-1-oxo-1,2-dihydroisoquinolin-7-yl)-2,3-dichlorobenzenesulfonamide	White solid, yield: 3.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.12 (dd, <i>J</i> = 8.0, 2.0 Hz, 2H), 7.85 (d, <i>J</i> = 9.0 Hz, 1H), 7.78 (s, 1H), 7.69 (d, <i>J</i> = 8.0 Hz, 1H), 7.40 (dd, <i>J</i> = 9.0, 2.2 Hz, 1H), 7.11 (d, <i>J</i> = 2.2 Hz, 1H), 6.39 (s, 1H).	448.2

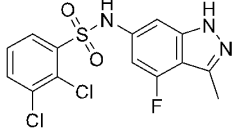
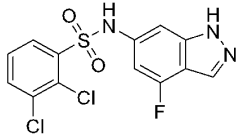
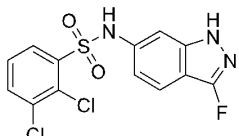
Example 58 Method 1	 2,3-dichloro-N-(3-methyl-1H-indazol-6-yl)benzenesulfonamide	white solid, yield: 52.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.43 (s, 1H), 10.86 (br s, 1H), 8.01 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.89 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.55 (d, <i>J</i> = 8.4 Hz, 1H), 7.51 (t, <i>J</i> = 8.0 Hz, 1H), 7.14 (d, <i>J</i> = 1.6 Hz, 1H), 6.88 (dd, <i>J</i> = 8.4, 1.6 Hz, 1H), 2.38 (s, 3H).	356.1
Example 59 Method 1	 N-(benzo[c]isothiazol-6-yl)-2,3-dichlorobenzenesulfonamide	white solid, yield: 54.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.21 (s, 1H), 9.64 (d, <i>J</i> = 1.1 Hz, 1H), 8.16 (dd, <i>J</i> = 8.0, 1.5 Hz, 1H), 7.92 (dd, <i>J</i> = 8.1, 1.5 Hz, 1H), 7.80 (d, <i>J</i> = 9.2 Hz, 1H), 7.58 (t, <i>J</i> = 8.0 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.13 (dd, <i>J</i> = 9.1, 2.0 Hz, 1H).	359.0
Example 60 Method 1	 2,3-dichloro-N-(quinolin-2-yl)benzenesulfonamide	white solid, yield: 33.7%	¹ H NMR (400 MHz, CDCl ₃) δ 12.24 (s, 1H), 8.22 (dd, <i>J</i> = 8.0, 1.5 Hz, 1H), 7.96 (d, <i>J</i> = 9.4 Hz, 1H), 7.73 – 7.65 (m, 2H), 7.63 (dd, <i>J</i> = 8.0, 1.4 Hz, 1H), 7.50 (t, <i>J</i> = 7.5 Hz, 1H), 7.43 (t, <i>J</i> = 7.6 Hz, 1H), 7.36 (t, <i>J</i> = 8.0 Hz, 1H), 6.91 (d, <i>J</i> = 9.3 Hz, 1H).	353.2

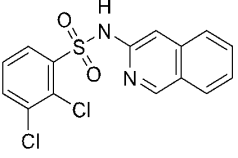
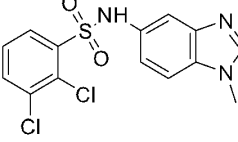
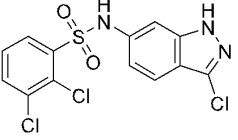
Example 61 Method 1	 2-fluoro-6-methyl-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 54.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.63 (s, 1H), 7.90 (s, 1H), 7.60 (s, 1H), 7.49 (td, <i>J</i> = 8.0, 5.5 Hz, 1H), 7.24 – 7.11 (m, 4H), 3.30 – 3.24 (m, 2H), 2.76 (t, <i>J</i> = 6.5 Hz, 2H), 2.59 (s, 3H).	335.1
Example 62 Method 1	 2,3-dichloro-N-(4-fluoro-1-oxo-1,2-dihydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 6.0%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.65 (d, <i>J</i> = 2.2 Hz, 1H), 8.14 (dd, <i>J</i> = 7.9, 1.5 Hz, 1H), 7.98 (s, 1H), 7.90 (dd, <i>J</i> = 8.1, 1.5 Hz, 1H), 7.77 (d, <i>J</i> = 8.9 Hz, 1H), 7.66 – 7.50 (m, 2H), 7.36 (dd, <i>J</i> = 8.8, 2.2 Hz, 1H), 2.40 (s, 3H).	387.1
Example 63 Method 1	 2,3-dichloro-N-(4-cyano-1-oxo-1,2-dihydroisoquinolin-7-yl)benzenesulfonamide	Brown solid, yield: 2.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.18 (d, <i>J</i> = 8.0 Hz, 1H), 8.09 (s, 1H), 7.85 (s, 1H), 7.79 – 7.69 (m, 3H), 7.46 (t, <i>J</i> = 8.0 Hz, 1H).	391.8

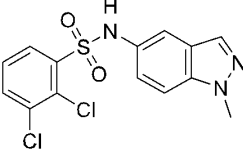
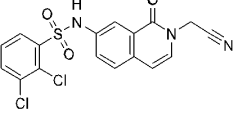
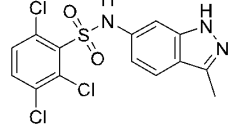
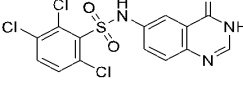
Example 64 Method 1	 2,3-dichloro-N-(3-oxazol-2-ylphenyl)benzenesulfonamide	White solid, yield: 46.6%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.09 (s, 1H), 8.21 (d, <i>J</i> = 0.8 Hz, 1H), 8.07 (dd, <i>J</i> = 8.0, 1.5 Hz, 1H), 7.93 (dd, <i>J</i> = 8.1, 1.5 Hz, 1H), 7.77 (t, <i>J</i> = 1.9 Hz, 1H), 7.66 – 7.60 (m, 1H), 7.56 (t, <i>J</i> = 8.0 Hz, 1H), 7.41 (t, <i>J</i> = 8.0 Hz, 1H), 7.37 (d, <i>J</i> = 0.8 Hz, 1H), 7.28 – 7.20 (m, 1H).	369.2
Example 65 Method 1	 N-(1-(2,3-dichlorophenyl)ethyl)pyrazolo[1,5-a]pyridin-6-amine	White solid, Yield: 23.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.80 (s, 1H), 8.35 (d, <i>J</i> = 1.6 Hz, 1H), 7.99 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.93 (dd, <i>J</i> = 6.8, 2.0 Hz, 2H), 7.63 (d, <i>J</i> = 9.4 Hz, 1H), 7.52 (t, <i>J</i> = 8.0 Hz, 1H), 7.00 (dd, <i>J</i> = 9.4, 2.0 Hz, 1H), 6.57 (d, <i>J</i> = 2.4 Hz, 1H).	342.1
Example 66 Method 1	 2,3-dichloro-N-(4-isopropyl-1-oxo-1,2-dihydroisoquinolin-7-yl)benzenesulfonamide	Yellow solid, Yield: 3.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.00 (s, 1H), 8.04 – 8.00 (m, 1H), 7.89 – 7.76 (m, 1H), 7.64 (d, <i>J</i> = 8.8 Hz, 1H), 7.52 – 7.41 (m, 2H), 6.71 (d, <i>J</i> = 5.6 Hz, 1H), 3.15 – 3.09 (m, 1H), 1.17 (d, <i>J</i> = 6.8 Hz, 6H).	410.9

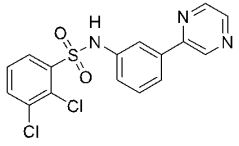
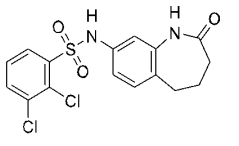
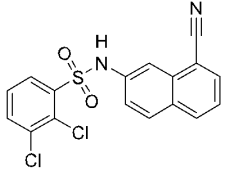
Example 67 Method 1			¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.98 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.86 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.48 (t, <i>J</i> = 8.0 Hz, 1H), 7.06 (d, <i>J</i> = 8.6 Hz, 2H), 6.98 (d, <i>J</i> = 8.6 Hz, 2H), 3.53 (s, 3H), 3.51 (s, 2H).	372.0 [M-H] ⁻
Example 68 Method 1	 2,3,6-trichloro-N-(1-oxo-1,2-dihydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 12.55 %	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.25 (s, 1H), 11.21 (s, 1H), 7.95 – 7.81 (m, 2H), 7.66 (d, <i>J</i> = 8.8 Hz, 1H), 7.59 (d, <i>J</i> = 8.7 Hz, 1H), 7.46 (dd, <i>J</i> = 8.7, 2.5 Hz, 1H), 7.07 (t, <i>J</i> = 6.4 Hz, 1H), 6.44 (d, <i>J</i> = 7.1 Hz, 1H).	403.3
Example 69 Method 1	 2,3-dichloro-4-fluoro-N-(1-oxo-1,2-dihydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 37.78 %	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.23 (d, <i>J</i> = 5.7 Hz, 1H), 11.13 (s, 1H), 8.10 (dd, <i>J</i> = 9.0, 5.6 Hz, 1H), 7.89 (d, <i>J</i> = 2.4 Hz, 1H), 7.63 (t, <i>J</i> = 8.6 Hz, 1H), 7.57 (d, <i>J</i> = 8.6 Hz, 1H), 7.46 (dd, <i>J</i> = 8.6, 2.4 Hz, 1H), 7.07 (dd, <i>J</i> = 7.1, 5.8 Hz, 1H), 6.44 (d, <i>J</i> = 7.1 Hz, 1H).	387.2

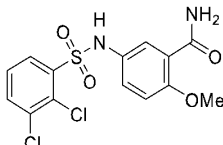
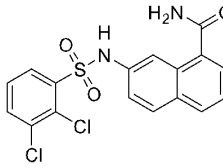
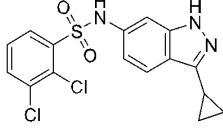
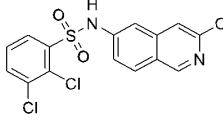
Example 70 Method 1	 2,3-dichloro-6-fluoro-N-(1-oxo-1,2-dihydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 10.42 %	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.31 (s, 1H), 11.24 (d, <i>J</i> = 5.7 Hz, 1H), 8.02 – 7.89 (m, 2H), 7.60 (d, <i>J</i> = 8.6 Hz, 1H), 7.54 – 7.45 (m, 2H), 7.08 (dd, <i>J</i> = 7.1, 5.7 Hz, 1H), 6.46 (d, <i>J</i> = 7.1 Hz, 1H).	387.2
Example 71 Method 1	 2,3-dichloro-N-(2-methylquinolin-7-yl)benzenesulfonamide		¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.24 (s, 1H), 8.15 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 8.10 (d, <i>J</i> = 8.4 Hz, 1H), 7.91 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.80 (d, <i>J</i> = 8.8 Hz, 1H), 7.58 (t, <i>J</i> = 8.0 Hz, 1H), 7.52 (d, <i>J</i> = 2.2 Hz, 1H), 7.33 (dd, <i>J</i> = 8.8, 2.2 Hz, 1H), 7.28 (d, <i>J</i> = 8.4 Hz, 1H), 2.58 (s, 3H).	367.1
Example 72 Method 1	 2,3-dichloro-N-(2,3-dimethyl-2H-indazol-6-yl)benzenesulfonamide		¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.66 (s, 1H), 8.01 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.87 (d, <i>J</i> = 8.0 Hz, 1H), 7.55 – 7.46 (m, 2H), 7.08 (s, 1H), 6.78 (d, <i>J</i> = 9.0 Hz, 1H), 3.93 (s, 3H), 3.33 (s, 3H).	370.1

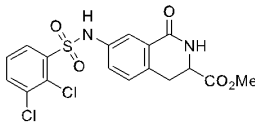
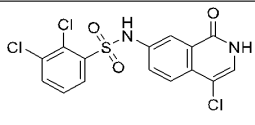
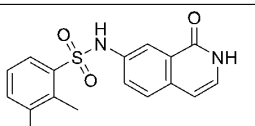
Example 73 Method 1	 2,3-dichloro-N-(4-fluoro-3-methyl-1H-indazol-6-yl)benzenesulfonamide		¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.71 (br, 1H), 11.08 (s, 1H), 8.06 (dd, <i>J</i> = 8.0, 1.5 Hz, 1H), 7.92 (dd, <i>J</i> = 8.1, 1.5 Hz, 1H), 7.56 (t, <i>J</i> = 8.1 Hz, 1H), 6.95 (d, <i>J</i> = 1.5 Hz, 1H), 6.63 (dd, <i>J</i> = 11.9, 1.5 Hz, 1H), 2.45 (s, 3H).	373.1
Example 74 Method 1	 2,3-dichloro-N-(4-fluoro-1H-indazol-6-yl)benzenesulfonamide		¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.18 (s, 1H), 11.13 (s, 1H), 8.07 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 8.06-8.04 (m, 1H), 7.92 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.56 (t, <i>J</i> = 8.0 Hz, 1H), 7.05 (t, <i>J</i> = 1.2 Hz, 1H), 6.71 (dd, <i>J</i> = 11.6, 1.6 Hz, 1H).	
Example 75 Method 1	 2,3-dichloro-N-(3-fluoro-1H-indazol-6-yl)benzenesulfonamide	White solid, yield: 18.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.06 (d, <i>J</i> = 6.8 Hz, 1H), 7.78 – 7.69 (m, 1H), 7.49 (d, <i>J</i> = 8.6 Hz, 1H), 7.39 (t, <i>J</i> = 8.0 Hz, 1H), 7.22 (s, 1H), 6.95 (dd, <i>J</i> = 8.6, 1.2 Hz, 1H).	359.9

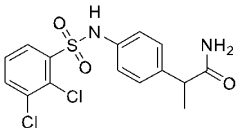
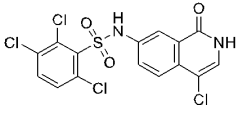
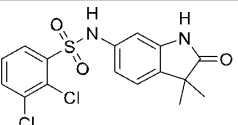
Example 76 Method 1	 2,3-dichloro-N-(isoquinolin-3-yl)benzenesulfonamide	Green solid, yield: 64.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.75 (s, 1H), 8.99 (s, 1H), 8.19 (dd, <i>J</i> = 8.0, 1.4 Hz, 1H), 7.98 (d, <i>J</i> = 8.2 Hz, 1H), 7.90 (dd, <i>J</i> = 8.0, 1.3 Hz, 1H), 7.85 (d, <i>J</i> = 8.2 Hz, 1H), 7.69 (t, <i>J</i> = 7.6 Hz, 1H), 7.58 (t, <i>J</i> = 8.0 Hz, 1H), 7.50 (t, <i>J</i> = 7.6 Hz, 1H), 7.40 (s, 1H).	352.9
Example 77 Method 1	 2,3-dichloro-N-(1-methyl-1H-benzo[d]imidazol-5-yl)benzenesulfonamide	white solid, yield: 14.8%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.56 (s, 1H), 8.14 (s, 1H), 7.93 (dd, <i>J</i> = 8.0, 1.4 Hz, 1H), 7.87 (dd, <i>J</i> = 8.0, 1.4 Hz, 1H), 7.50 – 7.41 (m, 2H), 7.34 (s, 1H), 7.06 (dd, <i>J</i> = 8.6, 1.6 Hz, 1H), 3.34 (s, 3H).	355.9
Example 78 Method 1	 2,3-dichloro-N-(3-chloro-1H-indazol-6-yl)benzenesulfonamide	white solid, yield: 17.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.08 (s, 1H), 11.12 (s, 1H), 8.06 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.92 (d, <i>J</i> = 8.0 Hz, 1H), 7.61 – 7.48 (m, 2H), 7.22 (d, <i>J</i> = 1.0 Hz, 1H), 7.03 (dd, <i>J</i> = 8.8, 1.6 Hz, 1H).	375.9

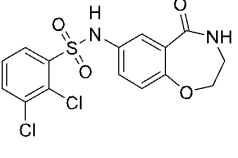
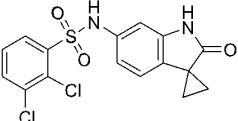
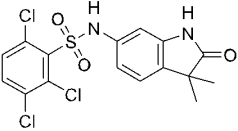
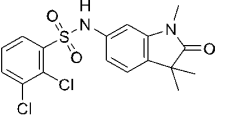
Example 79 Method 1	 2,3-dichloro-N-(1-methyl-1H-indazol-5-yl)benzenesulfonamide	white solid, yield: 63.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.59 (s, 1H), 7.97 (s, 1H), 7.92 (dd, <i>J</i> = 8.0, 1.2 Hz, 1H), 7.87 (dd, <i>J</i> = 8.0, 1.2 Hz, 1H), 7.53 (d, <i>J</i> = 8.8 Hz, 1H), 7.46 (dd, <i>J</i> = 9.4, 6.6 Hz, 2H), 7.17 (dd, <i>J</i> = 8.8, 2.0 Hz, 1H), 3.96 (s, 3H).	356.0
Example 80 Method 1	 2,3-dichloro-N-(2-(cyanomethyl)-1-oxo-1,2-dihydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 4.0%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.29 (s, 1H), 8.06 (dd, <i>J</i> = 8.0, 1.4 Hz, 1H), 7.92 – 7.86 (m, 2H), 7.59 – 7.47 (m, 3H), 7.40 (d, <i>J</i> = 7.4 Hz, 1H), 6.61 (d, <i>J</i> = 7.4 Hz, 1H), 5.03 (s, 2H).	409.0
Example 81 Method 1	 2,3,6-trichloro-N-(3-methyl-1H-indazol-6-yl)benzenesulfonamide	Light-yellow solid, yield: 6.3%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.50 (s, 1H), 11.03 (s, 1H), 7.85 (d, <i>J</i> = 8.8 Hz, 1H), 7.64 (d, <i>J</i> = 8.8 Hz, 1H), 7.57 (d, <i>J</i> = 8.6 Hz, 1H), 7.16 (d, <i>J</i> = 1.7 Hz, 1H), 6.87 (dd, <i>J</i> = 8.6, 1.8 Hz, 1H), 2.38 (s, 3H).	389.9
Example 82 Method 1	 2,3,6-trichloro-N-(4-oxo-3H-quinazolin-6-yl)benzenesulfonamide	Light-yellow solid, yield: 18.0%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.22 (s, 1H), 11.38 (s, 1H), 7.99 (d, <i>J</i> = 3.1 Hz, 1H), 7.89 (d, <i>J</i> = 8.7 Hz, 1H), 7.82 (d, <i>J</i> = 2.5 Hz, 1H), 7.68 (d, <i>J</i> = 8.8 Hz, 1H), 7.61 (d, <i>J</i> = 8.8 Hz, 1H), 7.55 (dd,	404.2

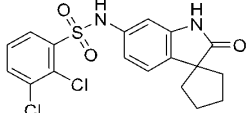
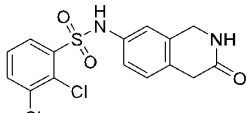
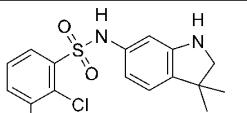
			$J = 8.8, 2.6 \text{ Hz, 1H}$).	
Example 83 Method 1	 2,3-dichloro-N-(3-pyrazin-2-ylphenyl)benzenesulfonamide	White solid, yield: 11.3%	$^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 11.01 (s, 1H), 9.12 (d, $J = 1.6 \text{ Hz, 1H}$), 8.72 (dd, $J = 2.5, 1.5 \text{ Hz, 1H}$), 8.62 (d, $J = 2.5 \text{ Hz, 1H}$), 8.08 (dd, $J = 8.0, 1.5 \text{ Hz, 1H}$), 7.93 – 7.87 (m, 2H), 7.81 – 7.75 (m, 1H), 7.54 (t, $J = 8.0 \text{ Hz, 1H}$), 7.41 (t, $J = 7.9 \text{ Hz, 1H}$), 7.29 – 7.19 (m, 1H).	380.25
Example 84 Method 1	 2,3-dichloro-N-(2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-8-yl)benzenesulfonamide	Yellow solid, yield: 77.2%	$^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 10.79 (s, 1H), 9.52 (s, 1H), 8.03 (dd, $J = 8.0, 1.5 \text{ Hz, 1H}$), 7.92 (dd, $J = 8.0, 1.5 \text{ Hz, 1H}$), 7.55 (t, $J = 8.0 \text{ Hz, 1H}$), 7.08 (d, $J = 8.0 \text{ Hz, 1H}$), 6.87 – 6.70 (m, 2H), 2.58 – 2.50 (m, 2H), 2.12 – 1.94 (m, 4H).	385.0
Example 85 Method 1	 2,3-dichloro-N-(8-cyanonaphthalen-2-yl)benzenesulfonamide	White solid, yield: 38.2%	$^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 11.51 (s, 1H), 8.18 (d, $J = 8.1 \text{ Hz, 2H}$), 8.09 (d, $J = 7.1 \text{ Hz, 1H}$), 8.04 (d, $J = 8.9 \text{ Hz, 1H}$), 7.94 (dd, $J = 8.2, 1.5 \text{ Hz, 1H}$), 7.78 (d, $J = 2.2 \text{ Hz, 1H}$), 7.60 (t, $J = 8.1 \text{ Hz, 1H}$), 7.57 – 7.46 (m, 2H).	377.1

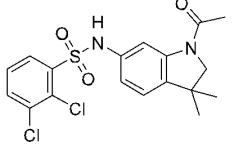
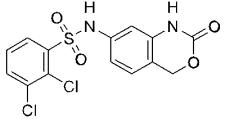
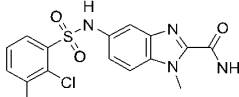
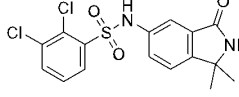
Example 86 Method 1	 5-((2,3-dichlorophenyl)sulfonylamido)-2-methoxybenzamide	White solid, yield: 40%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.58 (s, 1H), 7.92 (ddd, <i>J</i> = 8.4, 7.2, 1.6 Hz, 2H), 7.60 – 7.48 (m, 4H), 7.22 – 7.18 (m, 1H), 7.03 (d, <i>J</i> = 9.0 Hz, 1H), 3.80 (s, 3H).	375.0
Example 87 Method 1	 7-((2,3-dichlorophenyl)sulfonylamido)-1-naphthamide	White solid, yield: 15.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.19 (s, 1H), 8.09 (dd, <i>J</i> = 8.0, 1.5 Hz, 1H), 8.03 (s, 1H), 7.93 – 7.72 (m, 4H), 7.52 (q, <i>J</i> = 8.1, 7.5 Hz, 3H), 7.41 – 7.27 (m, 2H).	395.1
Example 88 Method 1	 2,3-dichloro-N-(3-cyclopropyl-1H-indazol-6-yl)benzenesulfonamide	White solid, yield: 25.6%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.36 (s, 1H), 10.85 (s, 1H), 8.01 (dd, <i>J</i> = 8.0, 1.4 Hz, 1H), 7.89 (dd, <i>J</i> = 8.1, 1.4 Hz, 1H), 7.61 (d, <i>J</i> = 8.6 Hz, 1H), 7.52 (t, <i>J</i> = 8.0 Hz, 1H), 7.13 (d, <i>J</i> = 1.6 Hz, 1H), 6.87 (dd, <i>J</i> = 8.8, 2.0 Hz, 1H), 2.23 – 2.10 (m, 1H), 0.99 – 0.77 (m, 4H).	382.0
Example 89 Method 1	 2,3-dichloro-N-(3-methoxyisoquinolin-6-yl)benzenesulfonamide	White solid, yield: 3.43%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.35 (s, 1H), 8.87 (s, 1H), 8.18 (dd, <i>J</i> = 8.0, 1.5 Hz, 1H), 7.95 – 7.87 (m, 2H), 7.57 (t, <i>J</i> = 8.0 Hz, 1H), 7.38 (d, <i>J</i> = 2.1 Hz, 1H), 7.21 (dd, <i>J</i> = 8.8, 2.1 Hz, 1H), 7.02	383.2

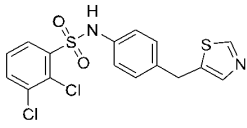
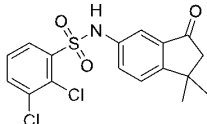
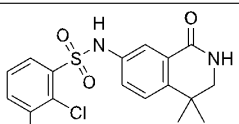
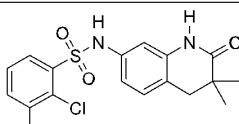
			(s, 1H), 3.89 (s, 3H).	
Example 90 Method 1 Mixture of Stereoisomers	 methyl 7-((2,3-dichlorophenyl)sulfonamido)-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate	White solid, yield: 26%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.94 (s, 1H), 8.18 (d, <i>J</i> = 4.2 Hz, 1H), 8.02 (dd, <i>J</i> = 8.0, 1.4 Hz, 1H), 7.93 (dd, <i>J</i> = 8.1, 1.5 Hz, 1H), 7.61 – 7.44 (m, 2H), 7.18 (s, 2H), 4.42 – 4.06 (m, 1H), 3.22 (dd, <i>J</i> = 16.3, 6.7 Hz, 1H), 3.02 (dd, <i>J</i> = 16.3, 3.4 Hz, 1H).	428.83
Example 91 Method 1	 2,3-dichloro-N-(4-chloro-1-oxo-1,2-dihydroisoquinolin-7-yl)benzenesulfonamide	Light-yellow solid, yield: 8.8%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.50 (d, <i>J</i> = 6.0 Hz, 1H), 11.27 (s, 1H), 8.07 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.95 (d, <i>J</i> = 2.4 Hz, 1H), 7.92 (dd, <i>J</i> = 8.1, 1.5 Hz, 1H), 7.73 (d, <i>J</i> = 8.8 Hz, 1H), 7.62 (dd, <i>J</i> = 8.8, 2.5 Hz, 1H), 7.56 (t, <i>J</i> = 8.1 Hz, 1H), 7.35 (d, <i>J</i> = 6.1 Hz, 1H).	403.3
Example 191 Method 1	 3-bromo-2-methyl-N-(1-oxo-1,2-dihydroisoquinolin-7-yl)benzenesulfonamide	Brown solid, yield: 73.8%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.21 (d, <i>J</i> = 5.7 Hz, 1H), 10.91 (s, 1H), 7.93 (dd, <i>J</i> = 8.0, 1.2 Hz, 1H), 7.90 – 7.83 (m, 2H), 7.55 (d, <i>J</i> = 8.6 Hz, 1H), 7.43 (dd, <i>J</i> = 8.6, 2.4 Hz, 1H), 7.31 (t, <i>J</i> = 8.0 Hz, 1H), 7.06 (dd, <i>J</i> = 7.0, 5.7 Hz, 1H), 6.44 (d, <i>J</i> = 7.0	390.8 [M-H] ⁻

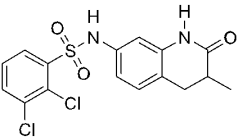
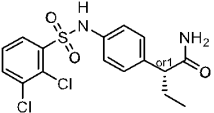
			Hz, 1H), 2.69 (s, 3H).	
Example 196 Method 1 Mixture of Stereoisomers	 2-(4-((2,3-dichlorophenyl)sulfonamido)phenyl)propanamide	White solid, yield: 10.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.73 (s, 1H), 8.02 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.91 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.53 (t, <i>J</i> = 8.0 Hz, 1H), 7.31 (s, 1H), 7.16 (d, <i>J</i> = 8.4 Hz, 2H), 7.01 (d, <i>J</i> = 8.4 Hz, 2H), 6.76 (s, 1H), 3.44 (q, <i>J</i> = 7.0 Hz, 1H), 1.21 (d, <i>J</i> = 7.0 Hz, 3H).	372.8
Example 197 Method 1	 2,3,6-trichloro-N-(4-chloro-1-oxo-1,2-dihydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 5.7 %	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.53 (d, <i>J</i> = 6.1 Hz, 1H), 11.48 (s, 1H), 7.97 (d, <i>J</i> = 2.4 Hz, 1H), 7.89 (d, <i>J</i> = 8.8 Hz, 1H), 7.75 (d, <i>J</i> = 8.8 Hz, 1H), 7.67 (d, <i>J</i> = 8.8 Hz, 1H), 7.61 (dd, <i>J</i> = 8.8, 2.5 Hz, 1H), 7.37 (d, <i>J</i> = 6.1 Hz, 1H).	436.8
Example 204 Method 1	 2,3-dichloro-N-(3,3-dimethyl-2-oxoindolin-6-yl)benzenesulfonamide	White solid, yield: 25.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.78 (s, 1H), 10.24 (s, 1H), 8.01 (dd, <i>J</i> = 7.9, 1.5 Hz, 1H), 7.92 (dd, <i>J</i> = 8.1, 1.5 Hz, 1H), 7.55 (t, <i>J</i> = 8.0 Hz, 1H), 7.11 (d, <i>J</i> = 7.9 Hz, 1H), 6.70 – 6.64 (m, 2H), 1.15 (s, 6H).	385.03

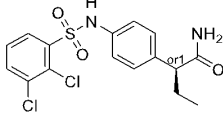
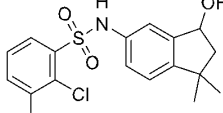
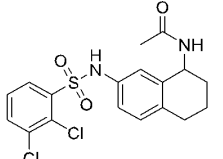
Example 206 Method 1	 2,3-dichloro-N-(5-oxo-3,4-dihydro-2H-1,4-benzoxazepin-7-yl)benzenesulfonamide	White solid, yield: 15.9%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.69 (s, 1H), 8.33 (t, <i>J</i> = 5.5 Hz, 1H), 8.00 – 7.86 (m, 2H), 7.56 – 7.49 (m, 2H), 7.18 (dd, <i>J</i> = 8.8, 2.9 Hz, 1H), 6.91 (d, <i>J</i> = 8.8 Hz, 1H), 4.20 (t, <i>J</i> = 4.8 Hz, 2H), 3.26 – 3.19 (m, 2H).	386.94
Example 208 Method 1	 2,3-dichloro-N-(2'-oxospiro[cyclopropane-1,3'-indolin]-6'-yl)benzenesulfonamide	White solid, yield: 41.3%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.67 (br s, 1H), 10.46 (br s, 1H), 7.96 (dd, <i>J</i> = 8.0, 1.5 Hz, 1H), 7.90 (dd, <i>J</i> = 8.1, 1.5 Hz, 1H), 7.52 (t, <i>J</i> = 8.0 Hz, 1H), 6.78 (d, <i>J</i> = 8.0 Hz, 1H), 6.72 (d, <i>J</i> = 1.9 Hz, 1H), 6.65 (dd, <i>J</i> = 8.0, 2.0 Hz, 1H), 1.48 – 1.40 (m, 2H), 1.38 – 1.30 (m, 2H).	383.3
Example 209 Method 1	 2,3,6-trichloro-N-(3,3-dimethyl-2-oxoindolin-6-yl)benzenesulfonamide	White solid, yield: 6.42%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.93 (s, 1H), 10.31 (s, 1H), 7.90 (d, <i>J</i> = 8.8 Hz, 1H), 7.68 (d, <i>J</i> = 8.8 Hz, 1H), 7.14 (d, <i>J</i> = 8.6 Hz, 1H), 6.77 – 6.59 (m, 2H), 1.16 (s, 6H).	419.3
Example 211 Method 1	 2,3-dichloro-N-(1,3,3-trimethyl-2-oxoindolin-6-yl)benzenesulfonamide	white solid, yield: 59.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.84 (s, 1H), 8.09 (dd, <i>J</i> = 8.0, 1.5 Hz, 1H), 7.93 (dd, <i>J</i> = 8.2, 1.5 Hz, 1H), 7.56 (t, <i>J</i> = 8.0 Hz, 1H), 7.18	399.3

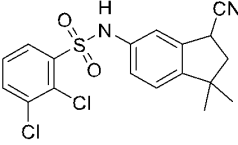
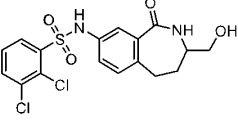
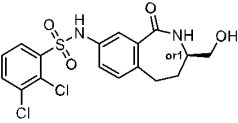
	de		(d, $J = 7.9$ Hz, 1H), 6.76 – 6.68 (m, 2H), 3.03 (s, 3H), 1.17 (s, 6H).	
Example 212 Method 1	 2,3-dichloro-N-(2'-oxospiro[cyclopentane-1,3'-indolin]-6'-yl)benzenesulfonamide	brown solid, yield: 52.9%	^1H NMR (400 MHz, DMSO- d_6) δ 10.78 (s, 1H), 10.20 (s, 1H), 8.01 (dd, $J = 7.9$, 1.5 Hz, 1H), 7.93 (dd, $J = 8.1$, 1.5 Hz, 1H), 7.56 (t, $J = 8.0$ Hz, 1H), 7.07 (d, $J = 7.9$ Hz, 1H), 6.70 – 6.62 (m, 2H), 1.93 – 1.78 (m, 6H), 1.70 – 1.57 (m, 2H).	411.3
Example 217 Method 1	 2,3-dichloro-N-(3-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 6.60%	^1H NMR (400 MHz, DMSO- d_6) δ 10.75 (s, 1H), 8.07 – 7.99 (m, 1H), 7.97 – 7.86 (m, 2H), 7.60 – 7.48 (m, 1H), 7.15 – 6.90 (m, 3H), 4.21 (s, 2H), 3.30 (s, 2H).	370.93
Example 219 Method 1	 2,3-dichloro-N-(3,3-dimethylindolin-6-yl)benzenesulfonamide	yellow solid.	^1H NMR (400 MHz, DMSO- d_6) δ 10.37 (s, 1H), 7.98 (dd, $J = 7.9$, 1.6 Hz, 1H), 7.91 (dd, $J = 8.0$, 1.5 Hz, 1H), 7.54 (t, $J = 8.0$ Hz, 1H), 6.77 (d, $J = 7.7$ Hz, 1H), 6.31 – 6.22 (m, 2H), 5.57 (s, 1H), 3.09 (d, $J = 1.5$ Hz, 2H), 1.12 (s, 6H).	371.3

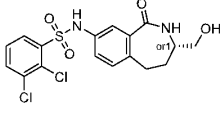
Example 220 Method 1	 N-(1-acetyl-3,3-dimethyl-indolin-6-yl)-2,3-dichlorobenzenesulfonamide	red solid, yield: 59.4%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.66 (s, 1H), 8.00 (dd, <i>J</i> = 8.0, 1.5 Hz, 1H), 7.95 – 7.85 (m, 2H), 7.54 (t, <i>J</i> = 8.0 Hz, 1H), 7.07 (d, <i>J</i> = 8.1 Hz, 1H), 6.75 (dd, <i>J</i> = 8.1, 2.1 Hz, 1H), 3.78 (s, 2H), 2.10 (s, 3H), 1.20 (s, 6H).	413.04
Example 224 Method 1	 2,3-dichloro-N-(2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-7-yl)benzenesulfonamide	white solid, yield: 12.23 %	¹ H NMR (400 MHz, DMSO) δ 10.88 (s, 1H), 10.11 (s, 1H), 8.01 (dd, <i>J</i> = 8.0, 1.1 Hz, 1H), 7.93 (d, <i>J</i> = 7.8 Hz, 1H), 7.56 (t, <i>J</i> = 8.0 Hz, 1H), 7.03 (d, <i>J</i> = 8.0 Hz, 1H), 6.71 (m, 2H), 5.14 (s, 2H).	373.0
Example 225 Method 1	 5-((2,3-dichlorophenyl)sulfonylamido)-1-methyl-1H-benzo[d]imidazole-2-carboxamide	White solid, yield: 19.0%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.60 (s, 1H), 8.17 (s, 1H), 7.95 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.82 (d, <i>J</i> = 7.6 Hz, 1H), 7.74 (s, 1H), 7.49 (d, <i>J</i> = 8.8 Hz, 1H), 7.44 (t, <i>J</i> = 8.0 Hz, 1H), 7.32 (s, 1H), 7.10 (d, <i>J</i> = 8.3 Hz, 1H), 4.01 (s, 3H).	398.9
Example 227 Method 1	 2,3-dichloro-N-(1,1-dimethyl-3-oxoisindolin-5-yl)benzenesulfonamide	White solid, yield: 38.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.03 (s, 1H), 8.67 (s, 1H), 8.06 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.94 (dd, <i>J</i> = 8.1, 1.5 Hz, 1H), 7.57 (t, <i>J</i> = 8.0 Hz, 1H), 7.50 (d, <i>J</i>	385.1

			= 8.1 Hz, 1H), 7.36 – 7.23 (m, 2H), 1.35 (s, 6H).	
Example 251 Method 1	 2,3-dichloro-N-(4-(thiazol-5-ylmethyl)phenyl)benzenesulfonamide	white solid, yield: 1.3%	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.74 (s, 1H), 7.88 (dd, <i>J</i> = 8.0, 1.5 Hz, 1H), 7.63 (dd, <i>J</i> = 8.0, 1.5 Hz, 1H), 7.49 (s, 1H), 7.28 (t, <i>J</i> = 8.0 Hz, 1H), 7.07 – 6.92 (m, 4H), 4.01 (s, 2H).	399.0
Example 264 Method 1	 2,3-dichloro-N-(1,1-dimethyl-3-oxo-2,3-dihydro-1H-inden-5-yl)benzenesulfonamide	white solid, yield: 26.9%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.67 (s, 1H), 8.01 (d, <i>J</i> = 1.4 Hz, 1H), 7.92 (s, 1H), 7.55 (s, 1H), 7.05 (d, <i>J</i> = 8.3 Hz, 2H), 6.96 (dd, <i>J</i> = 8.1, 2.0 Hz, 1H), 2.15 (dd, <i>J</i> = 12.5, 7.0 Hz, 1H), 1.62 (dd, <i>J</i> = 12.5, 7.2 Hz, 1H), 1.23 (s, 3H), 1.05 (s, 3H).	384
Example 265 Method 1	 2,3-dichloro-N-(4,4-dimethyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	white solid, yield: 36.2 %	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄): δ 8.06 (dd, <i>J</i> = 8.0 Hz, 1.6 Hz, 1H), 7.75 (dd, <i>J</i> = 8.4 Hz, 1.6 Hz, 1H), 7.71 (d, <i>J</i> = 2.4 Hz, 1H), 7.41 (t, <i>J</i> = 8.0 Hz, 1H), 7.35-7.27 (m, 2H), 3.20 (s, 2H), 1.26 (s, 6H).	398.9
Example 268 Method 1	 2,3-dichloro-N-(3,3-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl)benzenesulfonamide	White solid, yield: 49.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.67 (s, 1H), 9.99 (s, 1H), 7.99 (dd, <i>J</i> = 8.0, 1.5 Hz,	399.04

	dimethyl-2-oxo-1,4-dihydroquinolin-7-yl)benzenesulfonamide		¹ H), 7.92 (dd, <i>J</i> = 8.1, 1.5 Hz, 1H), 7.54 (t, <i>J</i> = 8.0 Hz, 1H), 6.98 (d, <i>J</i> = 8.1 Hz, 1H), 6.69 (d, <i>J</i> = 2.2 Hz, 1H), 6.62 (dd, <i>J</i> = 8.0, 2.2 Hz, 1H), 2.60 (s, 2H), 0.97 (s, 6H).	
Example 269 Method 1 Mixture of Stereoisomers	 2,3-dichloro-N-(3-methyl-2-oxo-3,4-dihydro-1H-quinolin-7-yl)benzenesulfonamide	White solid, yield: 12.7%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.69 (s, 1H), 10.02 (s, 1H), 8.00 (dd, <i>J</i> = 7.9, 1.5 Hz, 1H), 7.92 (dd, <i>J</i> = 8.1, 1.5 Hz, 1H), 7.54 (t, <i>J</i> = 8.0 Hz, 1H), 6.99 (d, <i>J</i> = 8.1 Hz, 1H), 6.69 (d, <i>J</i> = 2.2 Hz, 1H), 6.61 (dd, <i>J</i> = 8.1, 2.2 Hz, 1H), 2.79 (dd, <i>J</i> = 15.0, 5.4 Hz, 1H), 2.48 – 2.34 (m, 2H), 1.05 (d, <i>J</i> = 6.6 Hz, 3H).	385.03
Example 270 Method 1 single unknown stereoisomer	 rel-(R)-2-(4-((2,3-dichlorophenyl)sulfonamido)phenyl)butanamide	white solid, yield: 5.7%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.70 (s, 1H), 8.01 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.90 (dd, <i>J</i> = 8.2, 1.2 Hz, 1H), 7.53 (t, <i>J</i> = 8.0 Hz, 1H), 7.37 (s, 1H), 7.15 (d, <i>J</i> = 8.6 Hz, 2H), 7.00 (d, <i>J</i> = 8.6 Hz, 2H), 6.76 (s, 1H), 3.18 (m, 1H), 1.83 (m, 1H), 1.47 (m, 1H), 0.74 (t, <i>J</i> = 7.4 Hz, 3H).	386.9 Note: SFC Thar prep 80 CHIRALPA K AD-H 250mm × 20 mm, 5 μm Modifier : 40%EtOH (NH ₄ OH 0.2%) Rt=4.2 min

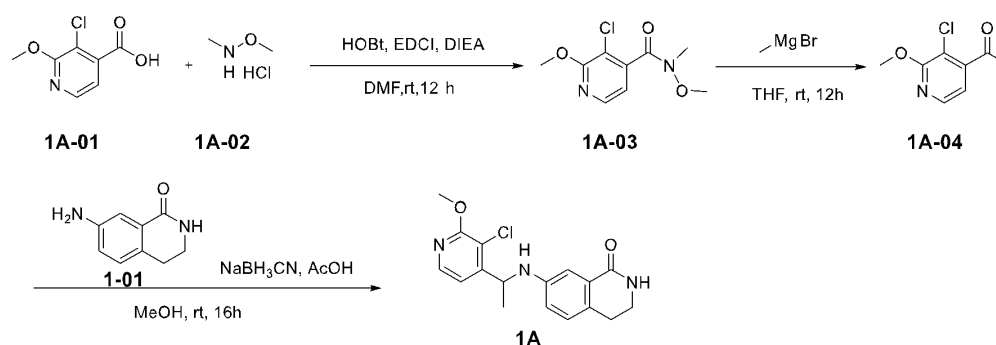
Example 270A Method 1 single unknown stereoisomer	 rel-(S)-2-(4-((2,3-dichlorophenyl)sulfonamido)phenyl)butanamide	white solid, yield: 4.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.70 (s, 1H), 8.01 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.90 (dd, <i>J</i> = 8.2, 1.2 Hz, 1H), 7.53 (t, <i>J</i> = 8.0 Hz, 1H), 7.37 (s, 1H), 7.15 (d, <i>J</i> = 8.6 Hz, 2H), 7.00 (d, <i>J</i> = 8.6 Hz, 2H), 6.76 (s, 1H), 3.18 (m, 1H), 1.83 (m, 1H), 1.47 (m, 1H), 0.74 (t, <i>J</i> = 7.4 Hz, 3H).	386.9 Note: SFC Thar prep 80 CHIRALPA K AD-H 250mm × 20 mm, 5 μm Modifier : 40%EtOH (NH ₄ OH 0.2%) Rt=3.74 min
Example 274 Method 1 Mixture of Stereoisomers	 2,3-dichloro-N-(3-hydroxy-1,1-dimethyl-2,3-dihydro-1H-inden-5-yl)benzenesulfonamide	white solid, yield: 25.8%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.67 (s, 1H), 8.02 (dd, <i>J</i> = 8.0, 1.5 Hz, 1H), 7.92 (dd, <i>J</i> = 8.1, 1.5 Hz, 1H), 7.55 (t, <i>J</i> = 8.0 Hz, 1H), 7.07 – 7.01 (m, 2H), 6.96 (dd, <i>J</i> = 8.1, 2.0 Hz, 1H), 5.21 (d, <i>J</i> = 6.2 Hz, 1H), 4.95 (q, <i>J</i> = 6.8 Hz, 1H), 2.15 (dd, <i>J</i> = 12.5, 7.0 Hz, 1H), 1.62 (dd, <i>J</i> = 12.5, 7.2 Hz, 1H), 1.23 (s, 3H), 1.05 (s, 3H).	386
Example 283 Method 1 Mixture of Stereoisomers	 N-(7-((2,3-dichlorophenyl)sulfonamido)-1,2,3,4-tetrahydronaphthalen-1-yl)acetamide	White solid, yield: 15.3%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.06 (d, <i>J</i> = 8.9 Hz, 1H), 6.81 (d, <i>J</i> = 8.3 Hz, 1H), 6.45 (dd, <i>J</i> = 8.4, 2.5 Hz, 1H), 6.40 – 6.28 (m, 2H), 4.83 (s, 1H), 4.57 (p, <i>J</i> = 6.6 Hz, 1H), 2.56-2.53 (m, 2H), 1.83 – 1.78 (m, 2H), 1.77 (s,	413.1

			3H), 1.49 (d, $J = 6.8$ Hz, 3H).	
Example 298 Method 1 Mixture of Stereoisomers	 2,3-dichloro-N-(3-cyano-1,1-dimethyl-2,3-dihydro-1H-inden-5-yl)benzenesulfonamide	white solid, yield: 51.9%	^1H NMR (400 MHz, DMSO- d_6) δ 10.86 (s, 1H), 8.05 (dd, $J = 7.9$, 1.5 Hz, 1H), 7.94 (dd, $J = 8.1$, 1.5 Hz, 1H), 7.56 (t, $J = 8.0$ Hz, 1H), 7.19 – 7.02 (m, 3H), 4.47 (t, $J = 8.0$ Hz, 1H), 2.30 (dd, $J = 12.5$, 8.1 Hz, 1H), 2.04 (dd, $J = 12.6$, 8.0 Hz, 1H), 1.26 (s, 3H), 1.09 (s, 3H).	395
Example 304A Method 1 Mixture of Stereoisomers	 2,3-dichloro-N-(3-(hydroxymethyl)-1-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yl)benzenesulfonamide	white solid, yield: 14.7%	^1H NMR (400 MHz, DMSO- d_6) δ 10.87 (s, 1H), 8.02 (dd, $J = 7.9$, 1.5 Hz, 1H), 7.93 (dd, $J = 8.1$, 1.5 Hz, 1H), 7.62 (d, $J = 5.2$ Hz, 1H), 7.55 (t, $J = 8.0$ Hz, 1H), 7.24 (t, $J = 1.5$ Hz, 1H), 7.13 (d, $J = 1.5$ Hz, 2H), 4.64 (t, $J = 5.8$ Hz, 1H), 3.38 (t, $J = 5.8$ Hz, 2H), 2.92-2.82 (m, 1H), 2.64-2.56 (m, 2H), 1.77-1.65 (m, 2H).	415.3
Example 304 Method 1 single unknown stereoisomer	 Rel-(S)-2,3-dichloro-N-(3-(hydroxymethyl)-1-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yl)benzenesulfonamide	white solid, yield 14.7%	^1H NMR (400 MHz, DMSO- d_6) δ 10.87 (s, 1H), 8.02 (dd, $J = 7.9$, 1.5 Hz, 1H), 7.93 (dd, $J = 8.1$, 1.5 Hz, 1H), 7.62 (d, $J = 5.2$ Hz, 1H), 7.55 (t, $J = 8.0$ Hz, 1H), 7.24 (t, $J = 1.5$ Hz, 1H), 7.13 (d, $J = 1.5$ Hz, 2H), 4.64 (t, $J = 5.8$ Hz, 1H), 3.38 (t, $J = 5.8$ Hz, 2H), 2.92-2.82 (m, 1H), 2.64-2.56 (m, 2H), 1.77-1.65 (m, 2H).	415.3

Example 304B Method 1 single unknown stereoisomer	 rel-(R)-2,3-dichloro-N-(3-(hydroxymethyl)-1-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yl)benzenesulfonamide	White solid, yield: 14.7%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.87 (s, 1H), 8.02 (dd, <i>J</i> = 7.9, 1.5 Hz, 1H), 7.93 (dd, <i>J</i> = 8.1, 1.5 Hz, 1H), 7.62 (d, <i>J</i> = 5.2 Hz, 1H), 7.55 (t, <i>J</i> = 8.0 Hz, 1H), 7.24 (t, <i>J</i> = 1.5 Hz, 1H), 7.13 (d, <i>J</i> = 1.5 Hz, 2H), 4.64 (t, <i>J</i> = 5.8 Hz, 1H), 3.38 (t, <i>J</i> = 5.8 Hz, 2H), 2.92-2.82 (m, 1H), 2.64-2.56 (m, 2H), 1.77-1.65 (m, 2H).	415.29
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Preparation of 6-(5-(pyridazin-3-ylamino)pyridin-3-yl)benzo[d]oxazol-2(3H)-one (1A)

Method 2



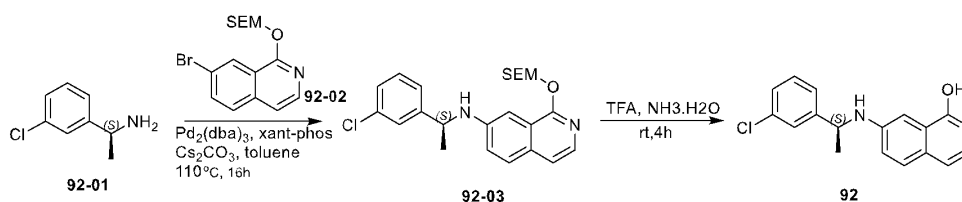
- 5 **Step 1:** A mixture of **1A-01** (500 mg, 5.33 mmol), **1A-02** (270 mg, 5.33 mmol), HOBt (720 mg, 5.33 mmol), EDCI (1.023 g, 5.33 mmol) and DIEA (2.07 g, 16 mmol) in DMF (10 mL) was stirred under N₂ at 25°C for 12 h. The reaction mixture was diluted with water. The aqueous phase was extracted with EA. The combined organic extracts were washed with brine and dried over Na₂SO₄. The solvent was removed under vacuum to give 600 mg of a crude
- 10 product **1A-03** that was used in the next step directly.
- Step 2:** **1A-03** (600 mg, 5.33 mmol) was dissolved in 10 mL of dry THF, methylmagnesium bromide (2 M in THF, 6 mL, 12 mmol) was added to the above solution at 0°C, and the mixture was stirred at rt for 12 h. The mixture was quenched with a saturated ammonium chloride solution and extracted with EA, washed with brine, dried over (Na₂SO₄), and
- 15 concentrated in vacuo. Purification by silica gel chromatography gave the compound **1A-04** (300 mg, 49%).

Step 3: **1A-04** (90 mg, 0.5mmol) was dissolved in 5 mL of dry MeOH, **1A-05** (240 mg, 1.5 mmol), NaBH₃CN (0.28 g, 4.5 mmol) and one drop of AcOH were added to the above solution, and the mixture was stirred for 12 h at r.t. The mixture was quenched with water and extracted with EA, washed with brine, dried over (Na₂SO₄), and concentrated in vacuo.

- 5 Purification by silica gel chromatography gave the titled compound **1A** (14 mg, 8.1%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.12 (d, *J* = 2.4 Hz, 1H), 7.87 (d, *J* = 2.4 Hz, 1H), 7.71 (s, 1H), 7.05 (s, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 6.22 (s, 1H), 4.56 (d, *J* = 6.8 Hz, 1H), 3.89 (s, 3H), 3.25 (td, *J* = 6.4, 2.8 Hz, 2H), 2.67 (t, *J* = 6.4 Hz, 2H), 1.41 (d, *J* = 6.8 Hz, 3H).

10 Preparation of

(S)-7-((1-(3-chlorophenyl)ethyl)amino)isoquinolin-1-ol (**92**)

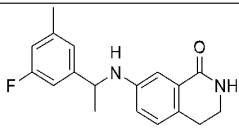
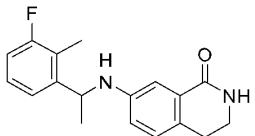
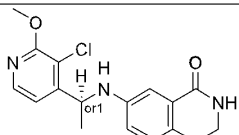


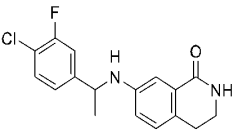
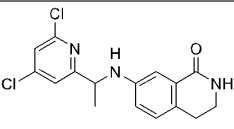
- Step 1:** A solution of **92-01** (200 mg, 1.29 mmol) in toluene (5 mL) under argon was added Pd₂(dba)₃ (590 mg, 0.64 mmol), Xant-phos (373 mg, 0.64 mmol), **92-02** (455mg, 1.28 mmol) and Cs₂CO₃ (1300 mg, 3.99 mmol), and the mixture was degassed with argon. The mixture was heated at 110 °C for 16h. Upon completion, the mixture was diluted with EtOAc, filtered through Celite and concentrated in vacuo. The crude product was purified by flash column chromatography to give the product **92-03**. MS (*m/z*): 429.1 (M+H⁺).

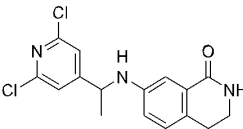
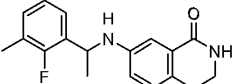
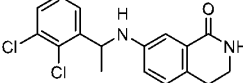
- Step 2** Compound **92-03** (200 mg, 0.46 mmol) in DCM (4 mL) was stirred at r.t. followed by addition of TFA (1 mL). The reaction mixture was stirred at 25 °C for 2 h and LCMS showed the reaction was completed. The solvent was removed in vacuo and NH₃·H₂O (2 mL) was added. The mixture was stirred at room temperature for 2 h. The residue was concentrated under vacuum and purified by prep-HPLC to afford **92** (45mg, 32.6 yield) as a light-yellow solid. MS (*m/z*): 299.0 [M+H]⁺. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.44 (t, *J* = 1.9 Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 1H), 7.37 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.24 – 7.17 (m, 2H), 7.13 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.89 (d, *J* = 7.0 Hz, 1H), 6.55 (d, *J* = 7.0 Hz, 1H), 4.62 (q, *J* = 6.8 Hz, 1H), 1.55 (d, *J* = 6.9 Hz, 3H).

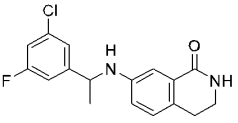
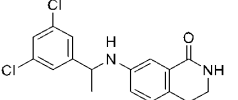
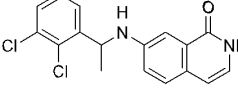
Examples (Compounds) **93-157**, **192-195**, **198-201A**, **203**, **205**, **210**, **213**, **221-223**, **237-237A**,

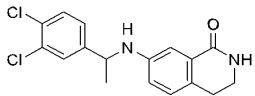
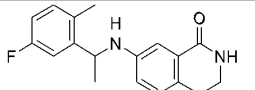
239A-239B, 244 and 254 were synthesized using a method like that used in Example 1A.

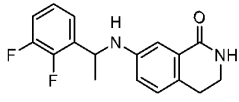
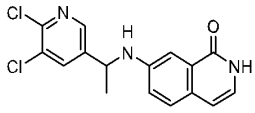
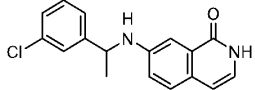
Example (Compound No.) Method	Structure and Name	Appearance and Yield	¹ H NMR Data	MS (m/z) [M+H] ⁺
Example 93 Method 2 Mixture of Stereoisomers	 7-((1-(3-fluoro-5-methylphenyl)ethyl)amino)-3,4-dihydroisoquinolin-1(2H)-one	White solid, yield: 7.96%	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.33 (s, 1H), 6.94 (d, <i>J</i> = 8.4 Hz, 2H), 6.87 (d, <i>J</i> = 9.6 Hz, 1H), 6.72 (d, <i>J</i> = 9.6 Hz, 1H), 6.60 (d, <i>J</i> = 8.0 Hz, 1H), 5.97 (s, 1H), 4.5 (q, <i>J</i> = 6.4 Hz, 1H), 3.48 (td, <i>J</i> = 6.8, 2.4 Hz, 2H), 2.84 (t, <i>J</i> = 6.4 Hz, 2H), 2.32 (s, 3H), 1.52 (d, <i>J</i> = 6.8 Hz, 3H).	299.1
Example 94 Method 2 Mixture of Stereoisomers	 2-((1-(3-fluoro-2-methylphenyl)ethyl)amino)-6,7-dihydro-1,7-naphthyridin-8(5H)-one	White solid, yield: 21%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.67 (br, 1H), 7.19 (dd, <i>J</i> = 1.6, 7.6 Hz, 1H), 7.15 – 7.09 (m, 1H), 7.00 – 6.93 (m, 2H), 6.91 (d, <i>J</i> = 8.4 Hz, 1H), 6.52 (dd, <i>J</i> = 8.4, 2.8 Hz, 1H), 6.31 (d, <i>J</i> = 6.8 Hz, 1H), 4.65 (t, <i>J</i> = 6.8 Hz, 1H), 3.26 (td, <i>J</i> = 6.4, 2.8 Hz, 2H), 2.64 (t, <i>J</i> = 6.4 Hz, 2H), 2.31 (d, <i>J</i> = 2.0 Hz, 3H), 1.37 (d, <i>J</i> = 6.8 Hz, 3H).	300.1
Example 95 Method 2 single unknown stereoisomer	 rel-(S)-7-((1-(3-chloro-2-methoxyphenyl)ethyl)amino)-3,4-dihydroisoquinolin-1(2H)-one	White solid, yield: 36%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.13 (d, <i>J</i> = 2.4 Hz, 1H), 7.87 (d, <i>J</i> = 2.4 Hz, 1H), 7.71 (s, 1H), 7.05 (d, <i>J</i> = 2.4	332.1 Note: SFC Thar prep 80 CHIRALPA

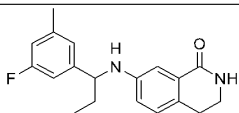
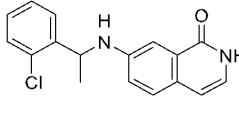
	methoxypyridin-4-yl)ethyl)amino)-3,4-dihydroisoquinolin-1(2H)-one		Hz, 1H), 6.96 (d, J = 8.0 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 6.22 (br, 1H), 4.57 (q, J = 6.4 Hz, 1H), 3.89 (s, 3H), 3.25 (td, J = 6.4, 2.8 Hz, 2H), 2.73 – 2.67 (t, J = 6.4 Hz, 2H), 1.42 (d, J = 6.8 Hz, 3H).	K AS-H 250mm*20 mm, 5 μ m Modifier: 40%ETOH (NH ₄ OH 0.2%). Rt = 4.17 min
Example 96 Method 2 Mixture of Stereoisomers	 7-((1-(4-chloro-3-fluorophenyl)ethyl)amino)-3,4-dihydroisoquinolin-1(2H)-one	White solid, yield: 6.7%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.68 (t, J = 2.8 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.39 (dd, J = 10.5, 2.0 Hz, 1H), 7.24 (dd, J = 8.2, 2.0 Hz, 1H), 7.02 (d, J = 2.6 Hz, 1H), 6.92 (d, J = 8.2 Hz, 1H), 6.61 (dd, J = 8.2, 2.6 Hz, 1H), 6.27 (d, J = 7.3 Hz, 1H), 4.53 (t, J = 6.9 Hz, 1H), 3.25 (td, J = 6.6, 2.7 Hz, 2H), 2.66 (t, J = 6.5 Hz, 2H), 1.40 (s, 3H).	319.3
Example 97 Method 2 Mixture of Stereoisomers	 7-((1-(4,6-dichloropyridin-2-yl)ethyl)amino)-3,4-dihydroisoquinolin-1(2H)-one	White solid, yield: 9.7%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.73 (s, 1H), 7.63 (d, J = 1.6 Hz, 1H), 7.49 (d, J = 1.6 Hz, 1H), 7.03 (d, J = 2.6 Hz, 1H), 6.97 (d, J = 8.2 Hz, 1H), 6.63 (dd, J = 8.2, 2.6 Hz, 1H), 4.52 (q, J = 6.8 Hz, 1H), 3.26 (td, J = 6.6, 2.8 Hz, 2H), 2.68 (t, J = 6.5 Hz, 2H), 1.44 (d, J = 6.8 Hz, 3H).	336.2

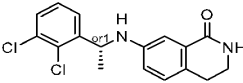
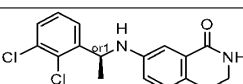
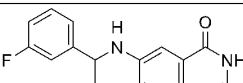
Example 98 Method 2 Mixture of Stereoisomer s	 7-((1-(2,6-dichloropyridin-4-yl)ethyl)amino)-3,4-dihydroisoquinolin-1(2H)-one	White solid, yield: 3.06%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.74 (d, <i>J</i> = 3.0 Hz, 1H), 7.58 (s, 2H), 7.02 (d, <i>J</i> = 2.6 Hz, 1H), 6.97 (d, <i>J</i> = 8.2 Hz, 1H), 6.63 (dd, <i>J</i> = 8.2, 2.6 Hz, 1H), 6.35 (d, <i>J</i> = 7.8 Hz, 1H), 4.63 (p, <i>J</i> = 6.8 Hz, 1H), 3.26 (dd, <i>J</i> = 6.6, 2.6 Hz, 2H), 2.68 (d, <i>J</i> = 6.6 Hz, 2H), 1.42 (d, <i>J</i> = 6.8 Hz, 3H).	336.2
Example 99 Method 2 Mixture of Stereoisomer s	 7-((1-(2-fluoro-3-methylphenyl)ethyl)amino)-3,4-dihydroisoquinolin-1(2H)-one	White solid, yield: 3.6%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.72 (s, 1H), 7.20 – 7.13 (m, 1H), 7.10 (d, <i>J</i> = 6.8 Hz, 1H), 7.02 – 6.95 (m, 2H), 6.92 (d, <i>J</i> = 8.2 Hz, 1H), 4.73 (p, <i>J</i> = 6.8 Hz, 1H), 3.24 (dd, <i>J</i> = 6.6, 2.8 Hz, 2H), 2.65 (d, <i>J</i> = 6.6 Hz, 2H), 2.24 (d, <i>J</i> = 2.0 Hz, 3H), 1.42 (d, <i>J</i> = 6.8 Hz, 3H).	299.2
Example 100 Method 2 Mixture of Stereoisomer s	 7-((1-(2,3-dichlorophenyl)ethyl)amino)-3,4-dihydroisoquinolin-1(2H)-one	White solid, yield: 5.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.72 (s, 1H), 7.49 (d, <i>J</i> = 1.6 Hz, 1H), 7.41 (d, <i>J</i> = 7.8 Hz, 1H), 7.30 (d, <i>J</i> = 7.8 Hz, 1H), 6.96 (d, <i>J</i> = 2.6 Hz, 1H), 6.93 (d, <i>J</i> = 8.2 Hz, 1H), 6.55 (d, <i>J</i> = 7.4 Hz, 1H), 6.49 (dd, <i>J</i> = 8.0, 2.6 Hz, 1H), 4.81 (p, <i>J</i> = 6.6 Hz, 1H), 3.27 – 3.19 (m, 2H), 2.65 (d, <i>J</i> = 6.4 Hz, 2H), 1.42 (d, <i>J</i> = 6.8 Hz, 3H).	335.3

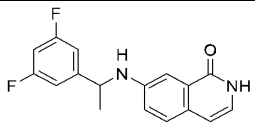
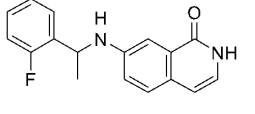
Example 101 Method 2 Mixture of Stereoisomers	 7-((1-(3-chloro-5-fluorophenyl)ethyl)amino)-3,4-dihydroisoquinolin-1(2H)-one	White solid, yield: 8.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.72 (s, 1H), 7.32 (s, 1H), 7.22 (d, <i>J</i> = 8.4 Hz, 2H), 7.02 (d, <i>J</i> = 2.6 Hz, 1H), 6.94 (d, <i>J</i> = 8.2 Hz, 1H), 6.62 (dd, <i>J</i> = 8.2, 2.6 Hz, 1H), 6.30 (d, <i>J</i> = 7.4 Hz, 1H), 4.55 (p, <i>J</i> = 6.8 Hz, 1H), 3.25 (td, <i>J</i> = 6.6, 2.6 Hz, 2H), 2.67 (t, <i>J</i> = 6.6 Hz, 2H), 1.39 (d, <i>J</i> = 6.6 Hz, 3H).	319.1
Example 102 Method 2 Mixture of Stereoisomers	 7-((1-(3,5-dichlorophenyl)ethyl)amino)-3,4-dihydroisoquinolin-1(2H)-one	White solid, yield: 10.7%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.72 (s, 1H), 7.44 (d, <i>J</i> = 2.0 Hz, 2H), 7.41 (t, <i>J</i> = 2.0 Hz, 1H), 7.02 (d, <i>J</i> = 2.6 Hz, 1H), 6.94 (d, <i>J</i> = 8.2 Hz, 1H), 6.62 (dd, <i>J</i> = 8.2, 2.6 Hz, 1H), 6.32 (d, <i>J</i> = 7.8 Hz, 1H), 4.56 (p, <i>J</i> = 7.0 Hz, 1H), 3.25 (td, <i>J</i> = 6.6, 2.8 Hz, 2H), 2.67 (t, <i>J</i> = 6.6 Hz, 2H), 1.39 (d, <i>J</i> = 6.8 Hz, 3H).	335.2
Example 103 Method 2 Mixture of Stereoisomers	 7-((1-(2,3-dichlorophenyl)ethyl)amino)isoquinolin-1(2H)-one	White solid, yield: 2.54%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.87 (d, <i>J</i> = 5.6 Hz, 1H), 7.50 (dd, <i>J</i> = 7.8, 1.6 Hz, 1H), 7.42 (dd, <i>J</i> = 7.8, 1.6 Hz, 1H), 7.35 (d, <i>J</i> = 8.4 Hz, 1H), 7.29 (t, <i>J</i> = 7.8 Hz, 1H), 7.02 – 6.96 (m, 2H), 6.87 (d, <i>J</i> = 7.0 Hz, 1H), 6.80 (dd, <i>J</i> = 7.0, 5.6 Hz, 1H), 6.32	333.2

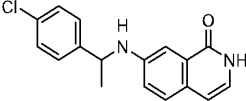
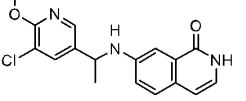
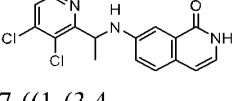
			(dd, $J = 7.0, 1.2$ Hz, 1H), 4.96 – 4.83 (m, 1H), 1.46 (d, $J = 6.6$ Hz, 3H).	
Example 104 Method 2 Mixture of Stereoisomers	 7-((1-(3,4-dichlorophenyl)ethyl)amino)-3,4-dihydroisoquinolin-1(2H)-one	White solid, yield: 3.6%	^1H NMR (400 MHz, DMSO- d_6) δ 7.71 (s, 1H), 7.62 (s, 1H), 7.55 (d, $J = 8.2$ Hz, 1H), 7.36 (d, $J = 2.0$ Hz, 1H), 7.01 (d, $J = 2.6$ Hz, 1H), 6.93 (d, $J = 8.2$ Hz, 1H), 6.61 (d, $J = 2.6$ Hz, 1H), 6.31 (d, $J = 7.4$ Hz, 1H), 4.53 (p, $J = 6.8$ Hz, 1H), 3.28 – 3.21 (m, 2H), 2.66 (d, $J = 6.4$ Hz, 2H), 1.39 (d, $J = 6.6$ Hz, 3H).	335.1
Example 105 Method 2 Mixture of Stereoisomers	 7-((1-(5-fluoro-2-methylphenyl)ethyl)amino)-3,4-dihydroisoquinolin-1(2H)-one	White solid, yield: 5.1%	^1H NMR (400 MHz, DMSO- d_6) δ 7.69 (s, 1H), 7.17 (dd, $J = 8.4, 6.0$ Hz, 1H), 7.09 (dd, $J = 10.6, 2.8$ Hz, 1H), 6.98 (d, $J = 2.6$ Hz, 1H), 6.96 – 6.79 (m, 2H), 6.51 (dd, $J = 8.2, 2.6$ Hz, 1H), 6.31 (d, $J = 7.2$ Hz, 1H), 4.65 – 4.51 (m, 1H), 3.24 (td, $J = 6.6, 2.8$ Hz, 2H), 2.65 (t, $J = 6.6$ Hz, 2H), 2.38	299.1

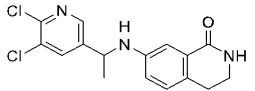
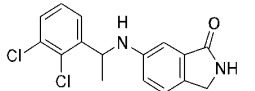
			(s, 3H), 1.35 (d, J = 6.6 Hz, 3H).	
Example 106 Method 2 Mixture of Stereoisomers	 7-((1-(2,3-difluorophenyl)ethyl)amino)-3,4-dihydroisoquinolin-1(2H)-one	White solid, yield: 4.9%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.71 (s, 1H), 7.30 – 7.08 (m, 3H), 7.02 (d, J = 2.6 Hz, 1H), 6.94 (d, J = 8.2 Hz, 1H), 6.60 (dd, J = 8.2, 2.6 Hz, 1H), 6.35 (d, J = 7.6 Hz, 1H), 4.78 (p, J = 7.0 Hz, 1H), 3.24 (td, J = 6.6, 2.6 Hz, 2H), 2.71 – 2.61 (m, 2H), 1.45 (d, J = 6.6 Hz, 3H).	303.3
Example 107 Method 2 Mixture of Stereoisomers	 7-((1-(5,6-dichloropyridin-3-yl)ethyl)amino)isoquinolin-1(2H)-one	White solid, yield: 1.9%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.91 (d, J = 5.6 Hz, 1H), 8.46 (d, J = 2.0 Hz, 1H), 8.14 (d, J = 2.0 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.13 – 7.05 (m, 2H), 6.83 (dd, J = 7.0, 5.6 Hz, 1H), 6.65 (d, J = 7.4 Hz, 1H), 6.36–6.32 (m, 1H), 4.76 (p, J = 6.8 Hz, 1H), 1.48 (d, J = 6.8 Hz, 3H).	334.2
Example 108 Method 2 Mixture of Stereoisomers	 7-((1-(3-chlorophenyl)ethyl)amino)isoquinolin-1(2H)-one	White solid, yield: 7.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.86 (d, J = 5.6 Hz, 1H), 7.46–7.42 (m, 1H), 7.39 – 7.31 (m, 3H), 7.26–7.21 (m, 1H), 7.10 – 7.02 (m, 2H), 6.80 (dd, J = 7.0, 5.6 Hz, 1H), 6.64 (d, J = 7.2 Hz, 1H), 6.32 (d, J = 7.0 Hz, 1H), 4.61 (p, J = 6.8 Hz, 1H), 1.44 (d, J =	299.2

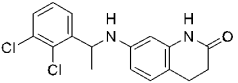
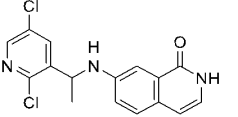
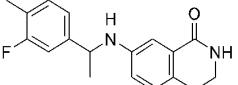
			6.6 Hz, 3H).	
Example 109 Method 2 Mixture of Stereoisomers	 7-((1-(3-fluoro-5-methylphenyl)propyl)amino)-3,4-dihydroisoquinolin-1(2H)-one	White solid, yield: 12.8%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.69 (d, <i>J</i> = 2.8 Hz, 1H), 7.05 (d, <i>J</i> = 2.4 Hz, 1H), 7.02 (d, <i>J</i> = 2.0 Hz, 1H), 6.95 (d, <i>J</i> = 10.0, 1H), 6.91 (d, <i>J</i> = 8.0 Hz, 1H), 6.81 (d, <i>J</i> = 10.0, 1H), 6.66 – 6.59 (m, 1H), 6.19 (d, <i>J</i> = 7.6 Hz, 1H), 4.23 (q, <i>J</i> = 7.2 Hz, 1H), 3.29 – 3.17 (m, 2H), 2.65 (t, <i>J</i> = 6.4 Hz, 2H), 2.28 (s, 3H), 1.81 – 1.57 (m, 2H), 0.90 (t, <i>J</i> = 7.2 Hz, 3H).	313.1
Example 110 Method 2 Mixture of Stereoisomers	 7-((1-(2-chlorophenyl)ethyl)amino)isoquinolin-1(2H)-one	White solid, yield: 4.02%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.85 (d, <i>J</i> = 4.8 Hz, 1H), 7.48-7.41 (m, 2H), 7.33 (d, <i>J</i> = 8.4 Hz, 1H), 7.29-7.19 (m, 2H), 7.04 – 6.96 (m, 2H), 6.83 – 6.75 (m, 2H), 6.31 (d, <i>J</i> = 6.8 Hz, 1H), 4.87 (p, <i>J</i> = 6.8 Hz, 1H), 1.45 (d, <i>J</i> = 6.8 Hz, 3H).	299.2

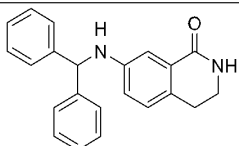
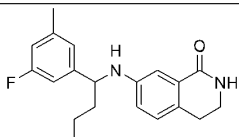
Example 111 Method 2 single unknown stereoisomer	 rel-(R)-7-((1-(2,3-dichlorophenyl)ethyl)amino)-3,4-dihydroisoquinolin-1(2H)-one	White solid, yield: 6.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.75-7.69 (m, 1H), 7.49 (dd, <i>J</i> = 7.8, 1.6 Hz, 1H), 7.40 (dd, <i>J</i> = 7.8, 1.7 Hz, 1H), 7.33-7.26 (m, 1H), 6.96 (d, <i>J</i> = 2.6 Hz, 1H), 6.93 (d, <i>J</i> = 8.2 Hz, 1H), 6.55 (d, <i>J</i> = 7.3 Hz, 1H), 6.48 (dd, <i>J</i> = 8.2, 2.6 Hz, 1H), 4.81 (p, <i>J</i> = 6.7 Hz, 1H), 3.23 (td, <i>J</i> = 6.7, 2.7 Hz, 2H), 2.65 (t, <i>J</i> = 6.6 Hz, 2H), 1.41 (d, <i>J</i> = 6.7 Hz, 3H).	335.1 Note: CHIRAL Cellulose SB, 2cm*25cm, 5μm, MTBE: (MeOH:DC M) =80:20 Rt = 5.480 min
Example 112 Method 2 single unknown stereoisomer	 rel-(R)-7-((1-(2,3-dichlorophenyl)ethyl)amino)-3,4-dihydroisoquinolin-1(2H)-one	White solid, yield: 6.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.75-7.69 (m, 1H), 7.49 (dd, <i>J</i> = 7.8, 1.6 Hz, 1H), 7.40 (dd, <i>J</i> = 7.8, 1.7 Hz, 1H), 7.33-7.26 (m, 1H), 6.96 (d, <i>J</i> = 2.6 Hz, 1H), 6.93 (d, <i>J</i> = 8.2 Hz, 1H), 6.55 (d, <i>J</i> = 7.3 Hz, 1H), 6.48 (dd, <i>J</i> = 8.2, 2.6 Hz, 1H), 4.81 (p, <i>J</i> = 6.7 Hz, 1H), 3.23 (td, <i>J</i> = 6.7, 2.7 Hz, 2H), 2.65 (t, <i>J</i> = 6.6 Hz, 2H), 1.41 (d, <i>J</i> = 6.7 Hz, 3H).	335.1 Note: CHIRAL Cellulose SB, 2cm*25cm, 5μm, MTBE: (MeOH:DC M) =80:20 Rt = 6.191 min
Example 113 Method 2 Mixture of Stereoisomers	 7-((1-(3-fluorophenyl)ethyl)amino)isoquinolin-1(2H)-one	White solid, yield: 10.9%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.85 (d, <i>J</i> = 5.6 Hz, 1H), 7.38 – 7.29 (m, 2H), 7.24 (d, <i>J</i> = 8.0 Hz, 1H), 7.19 (dt, <i>J</i> = 10.4, 2.4 Hz, 1H), 7.08 (d, <i>J</i> = 2.4 Hz,	283.2

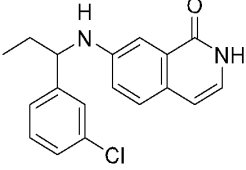
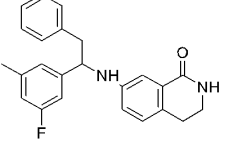
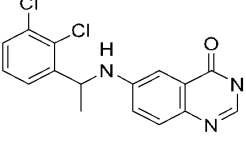
			1H), 7.05 (dd, $J = 8.4$, 2.4 Hz, 1H), 7.03 – 6.97 (m, 1H), 6.79 (dd, $J = 7.2$, 5.6 Hz, 1H), 6.62 (d, $J = 7.2$ Hz, 1H), 6.32 (dd, $J = 7.2$, 1.2 Hz, 1H), 4.61 (p, $J = 6.8$ Hz, 1H), 1.45 (d, $J = 6.8$ Hz, 3H).	
Example 114 Method 2 Mixture of Stereoisomers	 7-((1-(3,5-difluorophenyl)ethyl)amino)isoquinolin-1(2H)-one	White solid, yield: 12.9%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.88 (d, $J = 5.6$ Hz, 1H), 7.35 (d, $J = 8.4$ Hz, 1H), 7.19 – 6.98 (m, 5H), 6.81 (dd, $J = 7.2$, 5.6 Hz, 1H), 6.63 (d, $J = 7.3$ Hz, 1H), 6.33 (d, $J = 6.4$ Hz, 1H), 4.64 (p, $J = 6.8$ Hz, 1H), 1.44 (d, $J = 6.8$ Hz, 3H).	301.2
Example 115 Method 2 Mixture of Stereoisomers	 7-((1-(2-fluorophenyl)ethyl)amino)isoquinolin-1(2H)-one	White solid, yield: 10.8%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.87 (d, $J = 5.6$ Hz, 1H), δ 7.38 (td, $J = 7.6$, 1.6 Hz, 1H), 7.34 (d, $J = 8.4$ Hz, 1H), 7.28 – 7.15 (m, 2H), 7.11 (td, $J = 7.2$, 1.3 Hz, 1H), 7.05 (dd, $J = 10.4$, 2.0 Hz, 2H), 6.80 (dd, $J = 6.8$, 5.6 Hz, 1H), 6.65 (d, $J = 7.2$ Hz, 1H), 6.32 (d, $J = 6.8$ Hz, 1H), 4.83 (p, $J = 6.8$ Hz, 1H), 1.48 (d, $J = 6.8$ Hz, 3H).	283.2

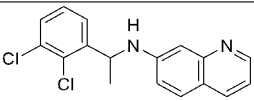
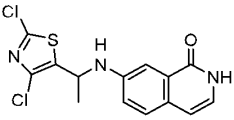
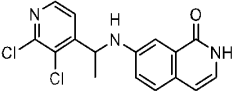
Example 116 Method 2 Mixture of Stereoisomers	 7-((1-(4-chlorophenyl)ethyl)amino)isoquinolin-1(2H)-one	White solid, yield: 13.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.85 (d, <i>J</i> = 5.6 Hz, 1H), 7.45 – 7.29 (m, 5H), 7.09-7.01 (m, 2H), 6.79 (t, <i>J</i> = 6.0 Hz, 1H), 6.63 (d, <i>J</i> = 6.8 Hz, 1H), 6.31 (d, <i>J</i> = 6.8 Hz, 1H), 4.58 (p, <i>J</i> = 6.8 Hz, 1H), 1.43 (d, <i>J</i> = 6.8 Hz, 3H).	299.1
Example 117 Method 2 Mixture of Stereoisomers	 7-((1-(5-chloro-6-methoxypyridin-3-yl)ethyl)amino)isoquinolin-1(2H)-one	White solid, yield: 9.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.89 (d, <i>J</i> = 5.6 Hz, 1H), 8.16 (d, <i>J</i> = 2.0 Hz, 1H), 7.89 (d, <i>J</i> = 2.0 Hz, 1H), 7.35 (d, <i>J</i> = 8.4 Hz, 1H), 7.12 (d, <i>J</i> = 2.4 Hz, 1H), 7.07 (dd, <i>J</i> = 8.6, 2.6 Hz, 1H), 6.81 (dd, <i>J</i> = 7.2, 5.6 Hz, 1H), 6.57 (d, <i>J</i> = 7.6 Hz, 1H), 6.33 (d, <i>J</i> = 6.8 Hz, 1H), 4.65 (p, <i>J</i> = 6.8 Hz, 1H), 3.89 (s, 3H), 1.46 (d, <i>J</i> = 6.8 Hz, 3H).	330.1
Example 118 Method 2 Mixture of Stereoisomers	 7-((1-(3,4-dichloropyridin-2-yl)ethyl)amino)isoquinolin-1(2H)-one	White solid, yield: 8.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.87 (d, <i>J</i> = 5.6 Hz, 1H), 8.44 (d, <i>J</i> = 5.2 Hz, 1H), 7.63 (d, <i>J</i> = 5.2 Hz, 1H), 7.34 (d, <i>J</i> = 8.4 Hz, 1H), 7.12 (d, <i>J</i> = 2.4 Hz, 1H), 7.09 (dd, <i>J</i> = 8.4, 2.4 Hz, 1H), 6.81 (dd, <i>J</i> = 6.8, 5.6 Hz, 1H), 6.63 (d, <i>J</i> = 8.8 Hz, 1H), 6.32 (d, <i>J</i> =	334.1

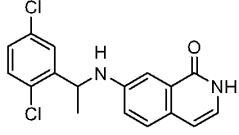
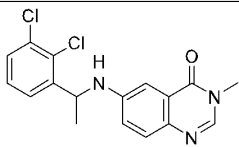
			6.8 Hz, 1H), 5.22-5.12 (m, 1H), 1.48 (d, $J = 6.8$ Hz, 3H).	
Example 119 Method 2 Mixture of Stereoisomers	 7-((1-(5,6-dichloropyridin-3-yl)ethyl)amino)-3,4-dihydroisoquinolin-1(2H)-one	White solid, yield: 9.3%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.42 (d, $J = 2.0$ Hz, 1H), 8.12 (d, $J = 2.0$ Hz, 1H), 7.74 (s, 1H), 7.04 (d, $J = 2.4$ Hz, 1H), 6.96 (d, $J = 8.0$ Hz, 1H), 6.66 (dd, $J = 8.0, 2.4$ Hz, 1H), 6.31 (s, 1H), 4.66 (q, $J = 6.4$ Hz, 1H), 3.25 (td, $J = 6.4, 2.8$ Hz, 3H), 2.67 (t, $J = 6.4$ Hz, 3H), 1.44 (d, $J = 6.8$ Hz, 3H).	337.1
Example 120 Method 2 Mixture of Stereoisomers	 6-((1-(2,3-dichlorophenyl)ethyl)amino)isoindolin-1-one	White solid, yield: 11.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.32 (s, 1H), 7.50 (dd, $J = 7.9, 1.6$ Hz, 1H), 7.41 (dd, $J = 7.9, 1.6$ Hz, 1H), 7.29 (t, $J = 7.9$ Hz, 1H), 7.20 (d, $J = 8.2$ Hz, 1H), 6.77 – 6.68 (m, 2H), 6.51 (d, $J = 2.2$ Hz, 1H), 4.84 (p, $J = 6.7$ Hz, 1H), 4.12 (s, 2H), 1.45 (d, $J = 6.6$ Hz, 3H).	321.1

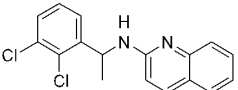
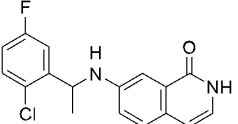
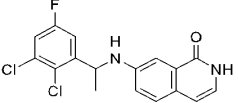
Example 121 Method 2 Mixture of Stereoisomers	 7-((1-(2,3-dichlorophenyl)ethyl)amino)-3,4-dihydroquinolin-2(1H)-one	White solid, yield: 10.4%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.87 (s, 1H), 7.48 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.39 (dd, <i>J</i> = 7.6, 1.6 Hz, 1H), 7.29 (t, <i>J</i> = 8.0 Hz, 1H), 6.76 (d, <i>J</i> = 8.0 Hz, 1H), 6.38 (d, <i>J</i> = 7.2 Hz, 1H), 5.99 (d, <i>J</i> = 2.4 Hz, 1H), 5.95 (dd, <i>J</i> = 8.0, 2.4 Hz, 1H), 4.72 (t, <i>J</i> = 6.8 Hz, 1H), 2.62 (t, <i>J</i> = 7.2 Hz, 2H), 2.34 – 2.28 (m, 2H), 1.39 (d, <i>J</i> = 6.8 Hz, 3H).	335.1
Example 122 Method 2 Mixture of Stereoisomers	 7-((1-(2,5-dichloropyridin-3-yl)ethyl)amino)isoquinolin-1(2H)-one	White solid, yield: 1.52%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.93 (d, <i>J</i> = 5.6 Hz, 1H), 8.40 (d, <i>J</i> = 2.6 Hz, 1H), 7.94 (d, <i>J</i> = 2.6 Hz, 1H), 7.39 (d, <i>J</i> = 8.4 Hz, 1H), 7.04 – 7.00 (m, 2H), 6.87 – 6.79 (m, 2H), 6.34 (d, <i>J</i> = 7.0 Hz, 1H), 4.80 (p, <i>J</i> = 6.8 Hz, 1H), 1.49 (d, <i>J</i> = 6.8 Hz, 3H).	334.2
Example 123 Method 2 Mixture of Stereoisomers	 7-((1-(3-fluoro-4-methylphenyl)ethyl)amino)-3,4-dihydroisoquinolin-1(2H)-one	White solid, yield: 9.9%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.69 (s, 1H), 7.18 (t, <i>J</i> = 8.0 Hz, 1H), 7.13 – 7.05 (m, 2H), 7.01 (d, <i>J</i> = 2.4 Hz, 1H), 6.91 (d, <i>J</i> = 8.0 Hz, 1H), 6.60 (dd, <i>J</i> = 8.0, 2.4 Hz, 1H), 6.22 (d, <i>J</i> = 7.2 Hz, 1H), 4.46 (p, <i>J</i> = 6.8 Hz, 1H), 3.24 (td, <i>J</i> = 6.4, 2.8 Hz, 2H), 2.68 – 2.62	299.2

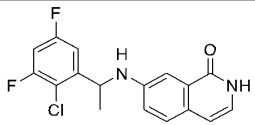
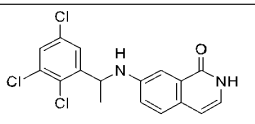
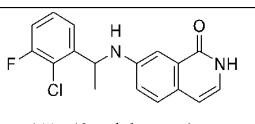
			(m, 2H), 2.16 (d, J = 1.6 Hz, 3H), 1.38 (d, J = 6.8 Hz, 3H).	
Example 124 Method 2	 7-(benzhydrylamino)-3,4-dihydroisoquinolin-1(2H)-one	white solid, yield: 1.73%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.70 (d, J = 3.2 Hz, 1H), 7.43 – 7.37 (m, 4H), 7.34 – 7.27 (m, 4H), 7.24 – 7.15 (m, 3H), 6.94 (d, J = 8.0 Hz, 1H), 6.80 (dd, J = 8.0, 2.4 Hz, 1H), 6.52 (d, J = 7.2 Hz, 1H), 5.65 (d, J = 7.2 Hz, 1H), 3.28 – 3.22 (m, 2H), 2.67 (t, J = 6.4 Hz, 2H).	329.3
Example 125 Method 2 Mixture of Stereoisomers	 7-((1-(3-fluoro-5-methylphenyl)butyl)amino)-3,4-dihydroisoquinolin-1(2H)-one	white solid, yield: 24.7%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.70 (d, J = 2.8 Hz, 1H), 7.05 (d, J = 2.4 Hz, 1H), 7.02 (s, 1H), 6.95 (d, J = 10.1, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 10.0 Hz, 1H), 6.63 (dd, J = 8.0, 2.4 Hz, 1H), 6.20 (d, J = 8.0 Hz, 1H), 4.39 – 4.24 (m, 1H), 3.29 – 3.17 (m, 2H), 2.65 (t, J = 6.4 Hz, 2H), 2.27 (s, 3H), 1.77 – 1.66 (m, 1H), 1.64 – 1.53 (m, 1H), 1.48 – 1.35 (m, 1H), 1.34 – 1.21 (m, 1H), 0.88 (t, J = 7.2 Hz, 3H).	327.2

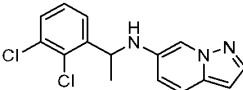
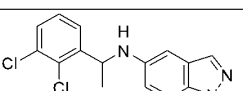
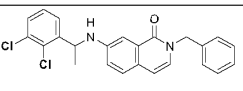
Example 126 Method 2 Mixture of Stereoisomers	 7-((1-(3-chlorophenyl)propyl)amino)isoquinolin-1(2H)-one	White solid, yield: 10.5%	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.40 (d, <i>J</i> = 2.0 Hz, 1H), 7.37 (d, <i>J</i> = 8.8 Hz, 1H), 7.33 (dt, <i>J</i> = 7.6, 1.2 Hz, 1H), 7.26 (t, <i>J</i> = 7.6 Hz, 1H), 7.22 (d, <i>J</i> = 2.4 Hz, 1H), 7.17 (dt, <i>J</i> = 7.6, 1.6 Hz, 1H), 7.12 (dd, <i>J</i> = 8.8, 2.4 Hz, 1H), 6.86 (d, <i>J</i> = 7.2 Hz, 1H), 6.51 (d, <i>J</i> = 7.2 Hz, 1H), 4.36 (dd, <i>J</i> = 7.6, 6.2 Hz, 1H), 1.96 – 1.72 (m, 2H), 1.00 (t, <i>J</i> = 7.6 Hz, 3H).	313.2
Example 127 Method 2 Mixture of Stereoisomers	 7-((1-(3-fluoro-5-methylphenyl)-2-phenylethyl)amino)-3,4-dihydroisoquinolin-1(2H)-one	White solid, yield: 5.16%	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.33 – 7.07 (m, 6H), 6.98 – 6.87 (m, 2H), 6.84 – 6.78 (m, 1H), 6.76 – 6.61 (m, 2H), 4.65 – 4.53 (m, 1H), 3.44 – 3.34 (m, 2H), 3.09 (dd, <i>J</i> = 13.4, 7.7 Hz, 1H), 2.97 (dd, <i>J</i> = 13.6, 6.7 Hz, 1H), 2.74 (td, <i>J</i> = 6.6, 2.7 Hz, 2H), 2.25 (s, 3H).	375.2
Example 128 Method 2 Mixture of Stereoisomers	 6-((1-(2,3-dichlorophenyl)ethyl)amino)quinazolin-4(3H)-one	White solid, yield: 11.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.86 (s, 1H), 7.74 (s, 1H), 7.51 (dd, <i>J</i> = 7.8, 1.6 Hz, 1H), 7.43 – 7.38 (m, 2H), 7.30 (t, <i>J</i> = 7.8 Hz, 1H), 7.09 (dd, <i>J</i> = 8.8, 2.8 Hz, 1H), 7.01 (d, <i>J</i> = 7.0 Hz, 1H), 6.82 (d, <i>J</i> = 2.8 Hz, 1H), 4.89 (t,	334.1

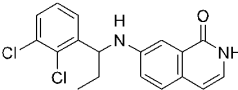
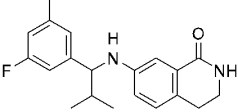
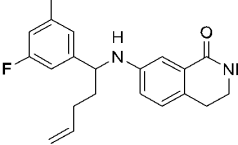
			$J = 6.8$ Hz, 1H), 1.46 (d, $J = 6.6$ Hz, 3H).	
Example 129 Method 2 Mixture of Stereoisomers	 N-(1-(2,3-dichlorophenyl)ethyl)quinolin-7-amine	White solid, yield: 18.8%	^1H NMR (400 MHz, DMSO- d_6) δ 8.57 (d, $J = 3.6$ Hz, 1H), 8.13 (d, $J = 7.8$ Hz, 1H), 7.70 (d, $J = 8.8$ Hz, 1H), 7.52 (dd, $J = 8.0, 1.4$ Hz, 1H), 7.44 (d, $J = 7.6$ Hz, 1H), 7.39 (br s, 1H), 7.30 (t, $J = 8.0$ Hz, 1H), 7.20 – 7.12 (m, 2H), 6.39 (s, 1H), 4.94 (p, $J = 6.4$ Hz, 1H), 1.51 (d, $J = 6.8$ Hz, 3H).	317.1
Example 130 Method 2 Mixture of Stereoisomers	 7-((1-(2,4-dichlorothiazol-5-yl)ethyl)amino)isoquinolin-1(2H)-one	White solid, yield: 5.7%	^1H NMR (400 MHz, DMSO- d_6) δ 10.96 (d, $J = 5.6$ Hz, 1H), 7.42 (d, $J = 8.4$ Hz, 1H), 7.14 (d, $J = 2.4$ Hz, 1H), 7.04 (dd, $J = 8.4, 2.4$ Hz, 1H), 6.87 (dd, $J = 7.2, 5.6$ Hz, 1H), 6.83 (d, $J = 5.2$ Hz, 1H), 6.37 (d, $J = 6.8$ Hz, 1H), 4.82 – 4.71 (m, 1H), 1.56 (d, $J = 6.8$ Hz, 3H).	340.1
Example 131 Method 2 Mixture of Stereoisomers	 7-((1-(2,3-dichloropyridin-4-yl)ethyl)amino)isoquinolin-1(2H)-one	White solid, yield: 7.3%	^1H NMR (400 MHz, DMSO- d_6) δ 10.90 (d, $J = 5.6$ Hz, 1H), 8.29 (d, $J = 4.8$ Hz, 1H), 7.45 (d, $J = 4.8$ Hz, 1H), 7.38 (d, $J = 8.4$ Hz, 1H), 7.00 (dd, $J = 8.4, 2.4$ Hz, 1H), 6.97 – 6.91 (m, 2H), 6.82 (dd, $J = 7.2, 5.6$ Hz, 1H), 6.33 (d, $J = 6.8$ Hz, 1H), 4.88 (p, $J = 6.8$ Hz, 3H).	334.2

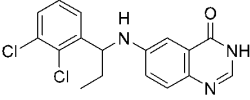
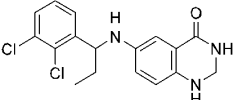
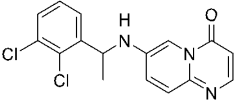
			1H), 1.48 (d, $J = 6.8$ Hz, 3H).	
Example 132 Method 2 Mixture of Stereoisomers	 7-((1-(2,5-dichlorophenyl)ethyl)amino)isoquinolin-1(2H)-one	White solid, yield: 9.3%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.89 (d, $J = 5.6$ Hz, 1H), 7.51 (d, $J = 8.5$ Hz, 1H), 7.47 (d, $J = 2.6$ Hz, 1H), 7.37 (d, $J = 9.1$ Hz, 1H), 7.31 (dd, $J = 8.5$, 2.6 Hz, 1H), 7.00 (d, $J = 7.6$ Hz, 2H), 6.87 – 6.76 (m, 2H), 6.33 (dd, $J = 7.1$, 1.3 Hz, 1H), 4.84 (p, $J = 6.7$ Hz, 1H), 1.45 (d, $J = 6.7$ Hz, 3H).	333.1
Example 133 Method 2 Mixture of Stereoisomers	 6-((1-(2,3-dichlorophenyl)ethyl)amino)-3-methylquinazolin-4(3H)-one	White solid, yield: 56.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.03 (s, 1H), 7.50 (dd, $J = 8.0$, 1.2 Hz, 1H), 7.44 – 7.37 (m, 2H), 7.29 (t, $J = 8.0$ Hz, 1H), 7.09 (dd, $J = 8.8$, 2.8 Hz, 1H), 7.04 (d, $J = 6.8$ Hz, 1H), 6.84 (d, $J = 2.8$ Hz, 1H), 4.89 (p, $J = 6.8$ Hz, 1H), 3.39 (s, 3H), 1.47 (d, $J = 6.4$ Hz, 3H).	348.2

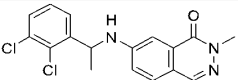
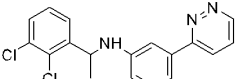
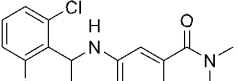
Example 134 Method 2 Mixture of Stereoisomers	 N-(1-(2,3-dichlorophenyl)ethyl)quinolin-2-amine	Off-white solid, yield: 78.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.86 (d, <i>J</i> = 8.8 Hz, 1H), 7.74 (d, <i>J</i> = 7.4 Hz, 1H), 7.59 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.47 (td, <i>J</i> = 7.6, 1.6 Hz, 2H), 7.41 (ddd, <i>J</i> = 8.4, 6.8, 1.6 Hz, 1H), 7.35 – 7.25 (m, 2H), 7.12 (ddd, <i>J</i> = 8.0, 6.8, 1.2 Hz, 1H), 6.84 (d, <i>J</i> = 8.8 Hz, 1H), 5.61 (p, <i>J</i> = 6.8 Hz, 1H), 1.46 (d, <i>J</i> = 6.8 Hz, 3H)	317.1
Example 135 Method 2 Mixture of Stereoisomers	 7-((1-(2-chloro-5-fluorophenyl)ethyl)amino)isoquinolin-1(2H)-one	White solid, yield: 3.84%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.89 (d, <i>J</i> = 5.6 Hz, 1H), 7.52 (dd, <i>J</i> = 8.8, 5.2 Hz, 1H), 7.37 (d, <i>J</i> = 9.2 Hz, 1H), 7.24 (dd, <i>J</i> = 9.6, 3.2 Hz, 1H), 7.11 (td, <i>J</i> = 8.4, 3.2 Hz, 1H), 7.06 – 6.96 (m, 2H), 6.88 – 6.71 (m, 2H), 6.33 (d, <i>J</i> = 7.0 Hz, 1H), 4.84 (m, 1H), 1.46 (d, <i>J</i> = 6.8 Hz, 3H).	316.7
Example 136 Method 2 Mixture of Stereoisomers	 7-((1-(2,3-dichloro-5-fluorophenyl)ethyl)amino)isoquinolin-1(2H)-one	White solid, yield: 1.73%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.91 (d, <i>J</i> = 5.6 Hz, 1H), 7.58 (dd, <i>J</i> = 8.0, 3.2 Hz, 1H), 7.38 (d, <i>J</i> = 8.4 Hz, 1H), 7.27 (dd, <i>J</i> = 9.2, 3.2 Hz, 1H), 7.05 – 6.95 (m, 2H), 6.92 – 6.77 (m, 2H), 6.34 (d, <i>J</i> = 7.2 Hz, 1H), 4.90 (p, <i>J</i> = 6.8 Hz, 1H), 1.46 (d,	351.2

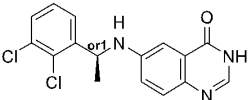
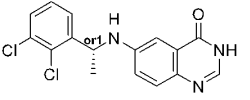
			$J = 6.8 \text{ Hz, 3H}$).	
Example 137 Method 2 Mixture of Stereoisomers	 7-((1-(2-chloro-3,5-difluorophenyl)ethyl)amino)isoquinolin-1(2H)-one	White solid, yield: 2.73%	$^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 10.90 (d, $J = 5.6 \text{ Hz, 1H}$), 7.39 (dd, $J = 9.6, 7.2 \text{ Hz, 2H}$), 7.15 (dt, $J = 9.6, 2.0 \text{ Hz, 1H}$), 7.01 (d, $J = 8.0 \text{ Hz, 2H}$), 6.83 (t, $J = 6.0 \text{ Hz, 2H}$), 6.34 (d, $J = 7.2 \text{ Hz, 1H}$), 4.90 (p, $J = 6.8 \text{ Hz, 1H}$), 1.47 (d, $J = 6.8 \text{ Hz, 3H}$).	334.7
Example 138 Method 2 Mixture of Stereoisomers	 7-((1-(2,3,5-trichlorophenyl)ethyl)amino)isoquinolin-1(2H)-one	White solid, yield: 1.10%	$^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 10.91 (d, $J = 5.6 \text{ Hz, 1H}$), 7.73 (d, $J = 2.4 \text{ Hz, 1H}$), 7.47 (d, $J = 2.4 \text{ Hz, 1H}$), 7.39 (d, $J = 8.4 \text{ Hz, 1H}$), 7.04 – 6.95 (m, 2H), 6.90 – 6.80 (m, 2H), 6.34 (d, $J = 7.0 \text{ Hz, 1H}$), 4.89 (p, $J = 6.8 \text{ Hz, 1H}$), 1.46 (d, $J = 6.8 \text{ Hz, 3H}$).	367.6
Example 139 Method 2 Mixture of Stereoisomers	 7-((1-(2-chloro-3-fluorophenyl)ethyl)amino)isoquinolin-1(2H)-one	White solid, yield: 10.2%	$^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 10.87 (d, $J = 5.6 \text{ Hz, 1H}$), 7.46 – 7.15 (m, 4H), 7.01 – 6.99 (m, 2H), 6.87 – 6.76 (m, 2H), 6.32 (d, $J = 7.0 \text{ Hz, 1H}$), 4.88 (p, $J = 6.8 \text{ Hz, 1H}$), 1.47 (d, $J = 6.8 \text{ Hz, 3H}$).	317.1

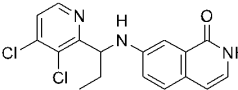
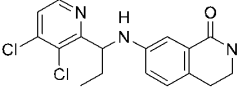
Example 140 Method 2 Mixture of Stereoisomers	 N-(1-(2,3-dichlorophenyl)ethyl)pyrazolo[1,5-a]pyridin-6-amine	White solid, yield: 9.7%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.61 (d, <i>J</i> = 2.4 Hz, 1H), 7.53 (dd, <i>J</i> = 7.8, 1.6 Hz, 1H), 7.51 – 7.42 (m, 2H), 7.33 (t, <i>J</i> = 7.6 Hz, 1H), 7.13 – 7.12 (m, 1H), 6.91 (dd, <i>J</i> = 9.6, 2.0 Hz, 1H), 6.47 (d, <i>J</i> = 6.8 Hz, 1H), 6.35 (d, <i>J</i> = 2.4 Hz, 1H), 4.74 (p, <i>J</i> = 6.8 Hz, 1H), 1.46 (d, <i>J</i> = 6.8 Hz, 3H).	306.2
Example 141 Method 2 Mixture of Stereoisomers	 N-(1-(2,3-dichlorophenyl)ethyl)-1-methyl-1H-indazol-5-amine	White solid, yield: 11.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.64 (s, 1H), 7.46 (ddd, <i>J</i> = 9.8, 7.8, 1.6 Hz, 2H), 7.35 (d, <i>J</i> = 8.8 Hz, 1H), 7.27 (t, <i>J</i> = 7.8 Hz, 1H), 6.91 (dd, <i>J</i> = 9.0, 2.0 Hz, 1H), 6.30 (d, <i>J</i> = 7.2 Hz, 1H), 6.21 (d, <i>J</i> = 2.0 Hz, 1H), 4.81 (p, <i>J</i> = 6.8 Hz, 1H), 3.89 (s, 3H), 1.44 (d, <i>J</i> = 6.8 Hz, 3H).	320.1
Example 142 Method 2 Mixture of Stereoisomers	 2-benzyl-7-((1-(2,3-dichlorophenyl)ethyl)amino)isoquinolin-1(2H)-one	White solid, yield: 11.4%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.50 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.42 (dd, <i>J</i> = 7.8, 1.6 Hz, 1H), 7.37 (d, <i>J</i> = 8.5 Hz, 1H), 7.34 – 7.16 (m, 7H), 7.07 – 6.98 (m, 2H), 6.95 (d, <i>J</i> = 7.0 Hz, 1H), 6.42 (d, <i>J</i> = 7.2 Hz, 1H), -5.16 - 5.01 (m, 2H), 4.90 (p, <i>J</i> = 6.8 Hz, 1H), 1.46 (d, <i>J</i> = 6.8 Hz, 3H).	423.2

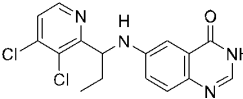
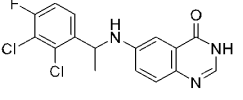
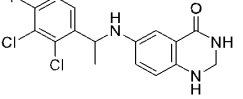
Example 143 Method 2 Mixture of Stereoisomers	 7-((1-(2,3-dichlorophenyl)propyl)amino)isoquinolin-1(2H)-one	White solid, yield: 12.4%	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.41 – 7.35 (m, 3H), 7.23 – 7.14 (m, 2H), 7.07 (dd, <i>J</i> = 8.4, 2.4 Hz, 1H), 6.86 (d, <i>J</i> = 7.2 Hz, 1H), 6.51 (d, <i>J</i> = 7.2 Hz, 1H), 4.84 – 4.80 (m, 1H), 1.96 – 1.71 (m, 2H), 1.10 (t, <i>J</i> = 7.2 Hz, 3H).	347.3
Example 144 Method 2 Mixture of Stereoisomers	 7-((1-(3-fluoro-5-methylphenyl)-2-methylpropyl)amino)-3,4-dihydroisoquinolin-1(2H)-one	White solid, yield: 4.00%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.68 (d, <i>J</i> = 2.9 Hz, 1H), 7.09 (d, <i>J</i> = 2.5 Hz, 1H), 7.00 (s, 1H), 6.94 (d, <i>J</i> = 9.4 Hz, 1H), 6.89 (d, <i>J</i> = 8.2 Hz, 1H), 6.81 (d, <i>J</i> = 9.7 Hz, 1H), 6.65 (dd, <i>J</i> = 8.2, 2.6 Hz, 1H), 6.11 (d, <i>J</i> = 8.3 Hz, 1H), 4.07 (t, <i>J</i> = 7.7 Hz, 1H), 3.29 – 3.20 (m, 2H), 2.64 (t, <i>J</i> = 6.5 Hz, 2H), 2.27 (s, 3H), 1.98 – 1.89 (m, 1H), 0.97 (d, <i>J</i> = 6.6 Hz, 3H), 0.79 (d, <i>J</i> = 6.7 Hz, 3H).	327.2
Example 145 Method 2 Mixture of Stereoisomers	 7-((1-(3-fluoro-5-methylphenyl)pent-4-en-1-yl)amino)-3,4-dihydroisoquinolin-1(2H)-one	white solid, yield: 11.0%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.70 (d, <i>J</i> = 3.2 Hz, 1H), 7.06 – 6.99 (m, 2H), 6.95 (d, <i>J</i> = 10.0, 1H), 6.91 (d, <i>J</i> = 8.0 Hz, 1H), 6.85 – 6.79 (m, 1H), 6.62 (dd, <i>J</i> = 8.2, 2.6 Hz, 1H), 6.25 (d, <i>J</i> = 8.0 Hz, 1H), 5.91 – 5.75 (m, 1H), 5.04 – 4.92 (m, 2H),	339.2

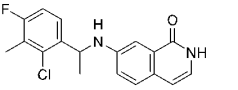
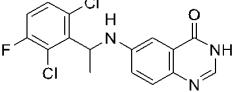
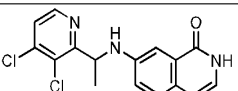
			4.36 – 4.28 (m, 1H), 3.28 – 3.19 (m, 2H), 2.65 (t, $J = 6.4$ Hz, 2H), 2.28 (s, 3H), 2.20 – 2.00 (m, 2H), 1.87 – 1.64 (m, 2H).	
Example 146 Method 2 Mixture of Stereoisomers	 6-[1-(2,3-dichlorophenyl)propylamino]-3H-quinazolin-4-one	White solid, yield: 6.7%	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.80 (s, 1H), 7.43 (d, $J = 8.8$ Hz, 1H), 7.41 – 7.34 (m, 2H), 7.20 (d, $J = 8.0$ Hz, 1H), 7.18 – 7.12 (m, 1H), 7.02 (d, $J = 2.8$ Hz, 1H), 4.84 – 4.80 (m, 1H), 1.96 – 1.72 (m, 2H), 1.10 (t, $J = 7.2$ Hz, 3H).	348.3
Example 147 Method 2 Mixture of Stereoisomers	 6-((1-(2,3-dichlorophenyl)propyl)amino)-2,3-dihydroquinazolin-4(1H)-one	White solid, yield: 8.7%	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.40 – 7.34 (m, 2H), 7.21 – 7.15 (m, 1H), 6.93 (d, $J = 2.4$ Hz, 1H), 6.68 – 6.56 (m, 2H), 4.73 (dd, $J = 8.0, 5.2$ Hz, 1H), 4.38 (s, 2H), 1.90 – 1.69 (m, 2H), 1.05 (t, $J = 7.2$ Hz, 3H).	350.3
Example 148 Method 2 Mixture of Stereoisomers	 7-((1-(2,3-dichlorophenyl)ethyl)amino)-4H-pyrido[1,2-a]pyrimidin-4-one	White solid, yield: 6.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.09 (d, $J = 6.0$ Hz, 1H), 7.70 – 7.61 (m, 2H), 7.61 – 7.51 (m, 2H), 7.44 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.33 (t, $J = 8.0$ Hz, 1H), 7.24 (d, $J = 6.6$ Hz, 1H), 6.15 (d, $J = 6.0$ Hz, 1H), 4.84 (p, $J = 6.6$ Hz, 1H), 1.50 (d, J	334.1

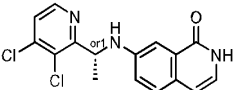
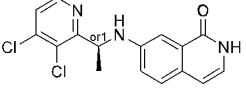
			= 6.6 Hz, 3H)	
Example 149 Method 2 Mixture of Stereoisomers	 7-((1-(2,3-dichlorophenyl)ethyl)amino)-2-methylphthalazin-1(2H)-one	White solid, yield: 9.9%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.06 (s, 1H), 7.61 (d, <i>J</i> = 8.6 Hz, 1H), 7.59 – 7.49 (m, 2H), 7.39 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.31 (t, <i>J</i> = 7.8 Hz, 1H), 7.10 (dd, <i>J</i> = 8.8, 2.4 Hz, 1H), 6.94 (s, 1H), 4.96 (p, <i>J</i> = 6.6 Hz, 1H), 3.60 (s, 3H), 1.49 (d, <i>J</i> = 6.6 Hz, 3H).	348.1
Example 150 Method 2 Mixture of Stereoisomers	 N-(1-(2,3-dichlorophenyl)ethyl)-3-(pyridazin-3-yl)aniline	yellow solid, yield: 6.8%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.16 (dd, <i>J</i> = 4.8, 1.6 Hz, 1H), 7.99 (dd, <i>J</i> = 8.8, 1.6 Hz, 1H), 7.73 (dd, <i>J</i> = 8.6, 4.8 Hz, 1H), 7.53 – 7.43 (m, 2H), 7.37 (s, 1H), 7.31 (t, <i>J</i> = 8.0 Hz, 1H), 7.23 – 7.16 (m, 2H), 6.74 (d, <i>J</i> = 7.2 Hz, 1H), 6.47 (dt, <i>J</i> = 6.8, 2.2 Hz, 1H), 4.93 (p, <i>J</i> = 6.8 Hz, 1H), 1.47 (d, <i>J</i> = 6.8 Hz, 3H).	344.0
Example 151 Method 2 Mixture of Stereoisomers	 7-((1-(2,6-dichlorophenyl)ethyl)amino)-2-methylisoquinolin-1(2H)-one	Light brown solid, yield: 5.8%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 6.49 (d, <i>J</i> = 8.6 Hz, 3H), 6.40 (t, <i>J</i> = 8.0 Hz, 1H), 6.30 (d, <i>J</i> = 2.4 Hz, 1H), 6.25 (d, <i>J</i> = 7.2 Hz, 1H), 6.19 (dd, <i>J</i> = 8.6, 2.6 Hz, 1H), 5.88 (d, <i>J</i> = 7.8 Hz, 1H), 5.52 (d, <i>J</i> = 7.2 Hz, 1H), 4.52 – 4.41 (m, 1H), 2.57 (s, 3H), 0.78 (d, <i>J</i> = 7.0	347.2

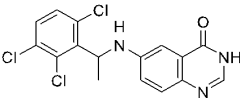
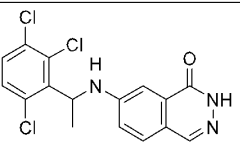
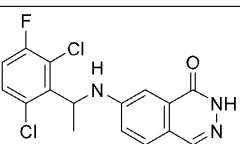
			Hz, 3H).	
Example 152 Method 2 single unknown stereoisomer	 rel-(R)-6-((1-(2,3-dichlorophenyl)ethyl)amino)quinazolin-4(3H)-one	White solid, yield: 9.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.86 (s, 1H), 7.75 (s, 1H), 7.51 (dd, <i>J</i> = 7.8, 1.6 Hz, 1H), 7.44 – 7.38 (m, 2H), 7.30 (t, <i>J</i> = 7.8 Hz, 1H), 7.09 (dd, <i>J</i> = 8.8, 2.8 Hz, 1H), 7.02 (d, <i>J</i> = 7.0 Hz, 1H), 6.82 (d, <i>J</i> = 2.8 Hz, 1H), 4.89 (q, <i>J</i> = 6.7 Hz, 1H), 1.47 (d, <i>J</i> = 6.6 Hz, 3H).	334.1 Note: Chiral separated from 128 . SFC Thar prep 80CHIRAL PAK WHELK-01 250mm*21 mm, 5μm Modifier : 40% ETOH (NH ₄ OH 0.2%). Rt = 3.64 min
Example 152A Method 2 single unknown stereoisomer	 Rel-(S)-6-((1-(2,3-dichlorophenyl)ethyl)amino)quinazolin-4(3H)-one	White solid, yield: 42.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.86 (s, 1H), 7.75 (s, 1H), 7.51 (dd, <i>J</i> = 7.8, 1.7 Hz, 1H), 7.46 – 7.38 (m, 2H), 7.30 (t, <i>J</i> = 7.9 Hz, 1H), 7.09 (dd, <i>J</i> = 8.8, 2.8 Hz, 1H), 7.02 (d, <i>J</i> = 7.0 Hz, 1H), 6.82 (d, <i>J</i> = 2.8 Hz, 1H), 4.89 (p, <i>J</i> = 6.7 Hz, 1H), 1.47 (d, <i>J</i> = 6.6 Hz, 3H).	334.1 Note: Chiral separated from 128 . SFC Thar prep 80CHIRAL PAK WHELK-01 250mm*21 mm, 5μm Modifier : 40% ETOH (NH ₄ OH 0.2%). Rt = 4.61 min

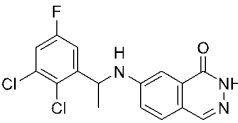
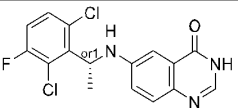
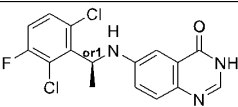
Example 153 Method 2 Mixture of Stereoisomers	 7-((1-(3,4-dichloropyridin-2-yl)propyl)amino)isoquinolin-1(2H)-one	yellow solid, yield: 8.6%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.85 (d, <i>J</i> = 5.4 Hz, 1H), 8.45 (d, <i>J</i> = 5.1 Hz, 1H), 7.62 (d, <i>J</i> = 5.1 Hz, 1H), 7.33 (d, <i>J</i> = 8.6 Hz, 1H), 7.16 (d, <i>J</i> = 2.5 Hz, 1H), 7.10 (dd, <i>J</i> = 8.6, 2.6 Hz, 1H), 6.80 (dd, <i>J</i> = 7.1, 5.7 Hz, 1H), 6.58 (d, <i>J</i> = 9.1 Hz, 1H), 6.31 (d, <i>J</i> = 6.9 Hz, 1H), 5.06 – 4.91 (m, 1H), 1.94 – 1.81 (m, 2H), 0.96 (t, <i>J</i> = 7.4 Hz, 3H).	348.3
Example 154 Method 2 Mixture of Stereoisomers	 7-((1-(3,4-dichloropyridin-2-yl)propyl)amino)-3,4-dihydroisoquinolin-1(2H)-one	White solid, yield: 10.4%	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.36 (d, <i>J</i> = 5.1 Hz, 1H), 7.44 (d, <i>J</i> = 5.1 Hz, 1H), 7.21 (d, <i>J</i> = 2.6 Hz, 1H), 6.98 (d, <i>J</i> = 8.2 Hz, 1H), 6.78 (dd, <i>J</i> = 8.2, 2.6 Hz, 1H), 5.07 (d, <i>J</i> = 6.8 Hz, 1H), 3.39 (t, <i>J</i> = 6.7 Hz, 2H), 2.78 (t, <i>J</i> = 6.7 Hz, 2H), 1.98 – 1.82 (m, 2H), 1.00 (t, <i>J</i> = 7.4 Hz, 3H).	350.3

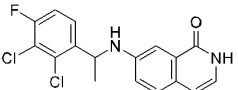
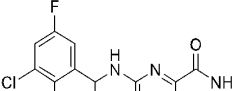
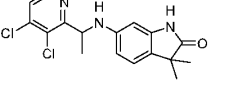
Example 155 Method 2 Mixture of Stereoisomers	 6-((1-(3,4-dichloropyridin-2-yl)propyl)amino)quinazolin-4(3H)-one	White solid, yield: 9.6%	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.37 (d, <i>J</i> = 5.1 Hz, 1H), 7.81 (s, 1H), 7.51 – 7.39 (m, 2H), 7.25 (dd, <i>J</i> = 8.8, 2.8 Hz, 1H), 7.19 (d, <i>J</i> = 2.8 Hz, 1H), 5.12 (t, <i>J</i> = 6.7 Hz, 1H), 2.01 – 1.90 (m, 2H), 1.04 (t, <i>J</i> = 7.4 Hz, 3H).	349.2
Example 156 Method 2 Mixture of Stereoisomers	 6-[1-(2,3-dichloro-4-fluorophenyl)ethylamino]-3H-quinazolin-4-one	White solid, yield: 11.2%	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.80 (s, 1H), 7.49 – 7.39 (m, 2H), 7.20 – 7.10 (m, 2H), 6.95 (d, <i>J</i> = 2.8 Hz, 1H), 4.96 (q, <i>J</i> = 6.7 Hz, 1H), 1.54 (d, <i>J</i> = 6.6 Hz, 3H).	352.2
Example 157 Method 2 Mixture of Stereoisomers	 6-((1-(2,3-dichloro-4-fluorophenyl)ethyl)amino)-2,3-dihydroquinazolin-4(1H)-one	yellow solid, yield: 12.7%	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.44 (dd, <i>J</i> = 8.8, 5.8 Hz, 1H), 7.12 (t, <i>J</i> = 8.6 Hz, 1H), 6.87 (s, 1H), 6.61 (s, 2H), 4.91 – 4.84 (m, 1H), 4.39 (s, 2H), 1.46 (d, <i>J</i> = 6.6 Hz, 3H).	354.3

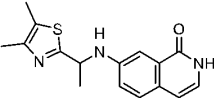
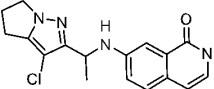
Example 192 Method 2 Mixture of Stereoisomers	 7-[1-(2-chloro-4-fluoro-3-methylphenyl)ethylamino]-2H-isoquinolin-1-one	White solid, yield: 26.01 %	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.82 (d, <i>J</i> = 5.6 Hz, 1H), 7.38 – 7.29 (m, 2H), 7.11 (t, <i>J</i> = 8.9 Hz, 1H), 7.03 – 6.95 (m, 2H), 6.83 – 6.72 (m, 2H), 6.31 (d, <i>J</i> = 7.0 Hz, 1H), 4.91 – 4.80 (m, 1H), 2.31 (d, <i>J</i> = 2.3 Hz, 3H), 1.44 (d, <i>J</i> = 6.6 Hz, 3H).	331.02
Example 193 Method 2 Mixture of Stereoisomers	 6-((1-(2,6-dichloro-3-fluorophenyl)ethyl)amino)quinazolin-4(3H)-one	white solid, yield: 23.0%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.82 (s, 1H), 7.74 (s, 1H), 7.59 – 7.42 (m, 1H), 7.41 – 7.32 (m, 2H), 7.12 (dd, <i>J</i> = 8.9, 2.7 Hz, 1H), 6.91 (d, <i>J</i> = 7.0 Hz, 2H), 5.28 (t, <i>J</i> = 7.1 Hz, 1H), 1.62 (d, <i>J</i> = 7.0 Hz, 3H).	352.0
Example 194 Method 2 Mixture of Stereoisomers	 7-((1-(3,4-dichloropyridin-2-yl)ethyl)amino)isoquinolin-1(2H)-one	White solid, yield: 15.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.86 (d, <i>J</i> = 5.6 Hz, 1H), 8.45 (d, <i>J</i> = 5.2 Hz, 1H), 7.63 (d, <i>J</i> = 5.1 Hz, 1H), 7.34 (d, <i>J</i> = 8.5 Hz, 1H), 7.12 (d, <i>J</i> = 2.5 Hz, 1H), 7.08 (dd, <i>J</i> = 8.5, 2.6 Hz, 1H), 6.81 (dd, <i>J</i> = 7.0, 5.7 Hz, 1H), 6.63 (d, <i>J</i> = 8.8 Hz, 1H), 6.32 (d, <i>J</i> = 7.0 Hz, 1H), 5.22 – 5.12 (m, 1H), 1.48 (d, <i>J</i> = 6.6 Hz, 3H).	334.0

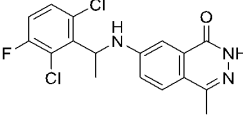
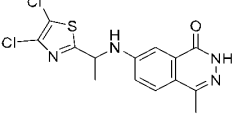
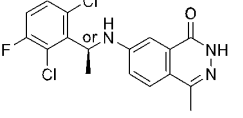
Example 194A Method 2 single unknown stereoisomer	 (S or R)-7-((1-(3,4-dichloropyridin-2-yl)ethyl)amino)isoquinolin-1(2H)-one	White solid, yield: 15.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.86 (d, <i>J</i> = 5.6 Hz, 1H), 8.45 (d, <i>J</i> = 5.2 Hz, 1H), 7.63 (d, <i>J</i> = 5.1 Hz, 1H), 7.34 (d, <i>J</i> = 8.5 Hz, 1H), 7.12 (d, <i>J</i> = 2.5 Hz, 1H), 7.08 (dd, <i>J</i> = 8.5, 2.6 Hz, 1H), 6.81 (dd, <i>J</i> = 7.0, 5.7 Hz, 1H), 6.63 (d, <i>J</i> = 8.8 Hz, 1H), 6.32 (d, <i>J</i> = 7.0 Hz, 1H), 5.22 – 5.12 (m, 1H), 1.48 (d, <i>J</i> = 6.6 Hz, 3H).	334.0 Note: Chiral separated from 118 , CHIRALPA K IC, 2cm*25cm, 5μm, Hex:DCM, EtOH, 20mL/min, Rt = 3.091 min
Example 194B Method 2 single unknown stereoisomer	 Rel-(R)-7-((1-(3,4-dichloropyridin-2-yl)ethyl)amino)isoquinolin-1(2H)-one	White solid,	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.86 (d, <i>J</i> = 5.6 Hz, 1H), 8.45 (d, <i>J</i> = 5.2 Hz, 1H), 7.63 (d, <i>J</i> = 5.1 Hz, 1H), 7.34 (d, <i>J</i> = 8.5 Hz, 1H), 7.12 (d, <i>J</i> = 2.5 Hz, 1H), 7.08 (dd, <i>J</i> = 8.5, 2.6 Hz, 1H), 6.81 (dd, <i>J</i> = 7.0, 5.7 Hz, 1H), 6.63 (d, <i>J</i> = 8.8 Hz, 1H), 6.32 (d, <i>J</i> = 7.0 Hz, 1H), 5.22 – 5.12 (m, 1H), 1.48 (d, <i>J</i> = 6.6 Hz, 3H).	334.0 Note: Chiral separated from 118 , CHIRALPA K IC, 2cm*25cm, 5μm, Hex:DCM, EtOH, 20mL/min, Rt = 4.151 min

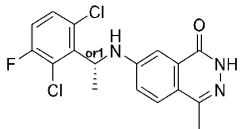
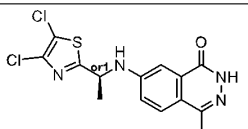
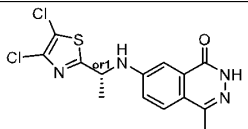
Example 195 Method 2 Mixture of Stereoisomers	 6-((1-(2,3,6-trichlorophenyl)ethyl)amino)quinazolin-4(3H)-one	White solid, yield: 10.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.81 (s, 1H), 7.73 (s, 1H), 7.56 (d, <i>J</i> = 8.2 Hz, 1H), 7.38 (d, <i>J</i> = 8.8 Hz, 1H), 7.11 (dd, <i>J</i> = 8.8, 2.8 Hz, 1H), 6.97 – 6.88 (m, 2H), 5.32 (q, <i>J</i> = 7.2 Hz, 1H), 1.61 (d, <i>J</i> = 7.0 Hz, 3H).	368.1
Example 198 Method 2 Mixture of Stereoisomers	 7-((1-(2,3,6-trichlorophenyl)ethyl)amino)phthalazin-1(2H)-one	White solid, yield: 9.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.81 (s, 1H), 7.73 (s, 1H), 7.56 (d, <i>J</i> = 8.2 Hz, 1H), 7.38 (d, <i>J</i> = 8.8 Hz, 1H), 7.11 (dd, <i>J</i> = 8.8, 2.8 Hz, 1H), 6.97 – 6.88 (m, 2H), 5.32 (q, <i>J</i> = 7.2 Hz, 1H), 1.61 (d, <i>J</i> = 7.0 Hz, 3H).	368.1
Example 199 Method 2 Mixture of Stereoisomers	 7-((1-(2,3,6-trichlorophenyl)ethyl)amino)phthalazin-1(2H)-one	White solid, yield: 9.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.81 (s, 1H), 7.73 (s, 1H), 7.56 (d, <i>J</i> = 8.2 Hz, 1H), 7.38 (d, <i>J</i> = 8.8 Hz, 1H), 7.11 (dd, <i>J</i> = 8.8, 2.8 Hz, 1H), 6.97 – 6.88 (m, 2H), 5.32 (q, <i>J</i> = 7.2 Hz, 1H), 1.61 (d, <i>J</i> = 7.0 Hz, 3H)	352.1

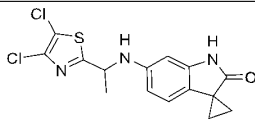
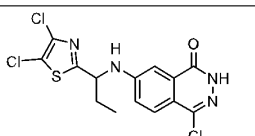
Example 200 Method 2 Mixture of Stereoisomers	 7-((1-(2,3-dichloro-5-fluorophenyl)ethyl)amino)phthalazin-1(2H)-one	White solid, yield: 10.3%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.25 (s, 1H), 8.04 (s, 1H), 7.66 – 7.58 (m, 2H), 7.48 (d, <i>J</i> = 7.0 Hz, 1H), 7.26 (dd, <i>J</i> = 9.3, 3.0 Hz, 1H), 7.11 (dd, <i>J</i> = 8.7, 2.5 Hz, 1H), 6.92 (s, 1H), 4.96 (q, <i>J</i> = 7.2 Hz, 1H), 1.49 (d, <i>J</i> = 6.6 Hz, 3H).	352.1
Example 201 Method 2 single unknown stereoisomer	 rel-(R)-6-((1-(2,6-dichloro-3-fluorophenyl)ethyl)amino)quinazolin-4(3H)-one	white solid, yield: 12.0%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.82 (s, 1H), 7.73 (s, 1H), 7.47 (s, 1H), 7.41 – 7.32 (m, 2H), 7.11 (dd, <i>J</i> = 8.8, 2.8 Hz, 1H), 6.97 – 6.86 (m, 2H), 5.27 (p, <i>J</i> = 7.1 Hz, 1H), 1.62 (d, <i>J</i> = 7.0 Hz, 3H).	352.0 Note: CHIRAL Cellulose SB , 2cm*25cm, 5μm, MeOH:DCM, MtBE, 20mL/min, Rt = 3.522 min
Example 201A Method 2 single unknown stereoisomer	 rel-(S)-6-((1-(2,6-dichloro-3-fluorophenyl)ethyl)amino)quinazolin-4(3H)-one	white solid, yield: 12%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.82 (s, 1H), 7.74 (s, 1H), 7.59 – 7.42 (m, 1H), 7.41 – 7.32 (m, 2H), 7.12 (dd, <i>J</i> = 8.9, 2.7 Hz, 1H), 6.91 (d, <i>J</i> = 7.0 Hz, 2H), 5.28 (t, <i>J</i> = 7.1 Hz, 1H), 1.62 (d, <i>J</i> = 7.0 Hz, 3H).	352.0 Note: CHIRAL Cellulose SB , 2cm*25cm, 5μm, MeOH:DCM, MtBE, 20mL/min, Rt = 1.69 min

Example 203 Method 2 Mixture of Stereoisomers	 7-[1-(2,3-dichloro-4-fluorophenyl)ethylamino]-2H-isoquinolin-1-one	white solid, yield: 24.5%	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.49 – 7.36 (m, 2H), 7.19 – 7.02 (m, 3H), 6.87 (d, <i>J</i> = 7.1 Hz, 1H), 6.52 (d, <i>J</i> = 7.1 Hz, 1H), 4.97 (q, <i>J</i> = 6.7 Hz, 1H), 1.53 (d, <i>J</i> = 6.6 Hz, 3H).	351.2
Example 205 Method 2 Mixture of Stereoisomers	 2-((1-(2,3-dichloro-5-fluorophenyl)ethyl)amino)-1,7-naphthyridin-8(7H)-one	White solid, yield: 18.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.13 (brs, 1H), 7.75 – 7.64 (m, 2H), 7.56 (dd, <i>J</i> = 8.0, 3.2 Hz, 1H), 7.34 (dd, <i>J</i> = 9.6, 3.2 Hz, 1H), 6.90 (t, <i>J</i> = 6.5 Hz, 2H), 6.30 (d, <i>J</i> = 6.9 Hz, 1H), 5.59 – 5.51 (m, 1H), 1.45 (d, <i>J</i> = 6.8 Hz, 3H).	352.4
Example 210 Method 2 Mixture of Stereoisomers	 6-((1-(3,4-dichloropyridin-2-yl)ethyl)amino)-3,3-dimethylindolin-2-one	white solid, yield: 15.04 %	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.01 (s, 1H), 8.46 (d, <i>J</i> = 5.2 Hz, 1H), 7.63 (d, <i>J</i> = 5.2 Hz, 1H), 6.86 (d, <i>J</i> = 8.0 Hz, 1H), 6.18 (d, <i>J</i> = 8.8 Hz, 1H), 6.12 (d, <i>J</i> = 2.0 Hz, 1H), 6.07 (dd, <i>J</i> = 8.0, 2.0 Hz, 1H), –5.06 – 4.97 (m, 1H), 1.42 (d, <i>J</i> = 6.8 Hz, 3H), 1.12 (d, <i>J</i> = 3.2 Hz, 6H).	350.0/352.0

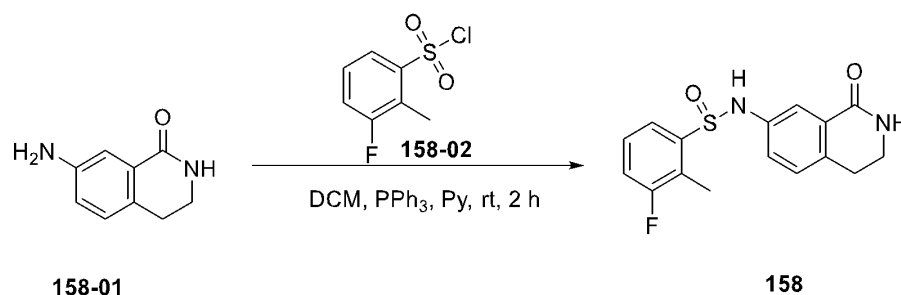
Example 213 Method 2 Mixture of Stereoisomers	 7-((1-(4,5-dimethylthiazol-2-yl)ethyl)amino)isoquinolin-1(2H)-one	white solid, yield: 15.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.91 (d, <i>J</i> = 5.5 Hz, 1H), 7.38 (d, <i>J</i> = 8.6 Hz, 1H), 7.16 (d, <i>J</i> = 2.5 Hz, 1H), 7.08 (dd, <i>J</i> = 8.6, 2.6 Hz, 1H), 6.84 (dd, <i>J</i> = 7.0, 5.6 Hz, 1H), 6.75 (d, <i>J</i> = 6.3 Hz, 1H), 6.35 (d, <i>J</i> = 7.0 Hz, 1H), 4.72 (p, <i>J</i> = 6.6 Hz, 1H), 2.25-2.20 (m, 6H), 1.53 (d, <i>J</i> = 6.7 Hz, 3H).	300.2
Example 221 Method 2 Mixture of Stereoisomers	 7-((1-(3-chloro-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-2-yl)ethyl)amino)isoquinolin-1(2H)-one	white solid, yield: 3.7%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.86 (d, <i>J</i> = 5.6 Hz, 1H), 8.15 (s, 1H), 7.33 (d, <i>J</i> = 8.8 Hz, 1H), 7.24 (d, <i>J</i> = 2.4 Hz, 1H), 7.08 (dd, <i>J</i> = 8.8, 2.4 Hz, 1H), 6.81 (dd, <i>J</i> = 7.2, 5.6 Hz, 1H), 6.33 (dd, <i>J</i> = 7.6, 2.8 Hz, 2H), 4.62 (q, <i>J</i> = 7.2 Hz, 1H), 4.08 – 3.96 (m, 2H), 2.79 (dd, <i>J</i> = 8.0, 6.4 Hz, 2H), 2.49 – 2.44 (m, 2H), 1.49 (d, <i>J</i> = 6.8 Hz, 3H).	329.0/331.0

Example 222 Method 2 Mixture of Stereoisomers	 7-((1-(2,6-dichloro-3-fluorophenyl)ethyl)amino)-4-methylphthalazin-1(2H)-one	Yellow solid, yield: 34.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.93 (br s, 1H), 7.60 (dd, <i>J</i> = 9.1, 1.3 Hz, 1H), 7.47 (br s, 1H), 7.44 – 7.32 (m, 2H), 7.07 (d, <i>J</i> = 5.9 Hz, 2H), 5.32 (t, <i>J</i> = 6.9 Hz, 1H), 2.34 (s, 3H), 1.63 (d, <i>J</i> = 7.0, 3H).	366.2
Example 223 Method 2 Mixture of Stereoisomers	 7-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-4-methylphthalazin-1(2H)-one	Yellow solid, yield: 31.4%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.09 (br s, 1H), 7.70 (d, <i>J</i> = 8.6 Hz, 1H), 7.52 (d, <i>J</i> = 6.3 Hz, 1H), 7.28 – 7.17 (m, 2H), 5.00 (t, <i>J</i> = 6.6 Hz, 1H), 2.40 (s, 3H), 1.59 (d, <i>J</i> = 6.7 Hz, 3H).	355.1
Example 237 Method 2 single unknown stereoisomer	 4-methyl-7-(((1S)-1-(2,6-dichloro-3-fluorophenyl)ethyl)amino)-2H-phthalazin-1-one	Yellow solid, yield: 35.2%	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.64 (d, <i>J</i> = 8.8 Hz, 1H), 7.42 – 7.31 (m, 1H), 7.23 (d, <i>J</i> = 2.6 Hz, 1H), 7.18 – 7.08 (m, 2H), 5.55 – 5.40 (m, 1H), 2.44 (s, 3H), 1.71 (d, <i>J</i> = 7.0 Hz, 3H).	366.2 Note: SFC CHIRALPA K AD - 3 250mm × 20 mm, 5 μ m Modifier: Hex(0.1%D EA):EtOH= 70:30 Rt=4.2 min

Example 237A Method 2 single unknown stereoisomer	 (R)-7-((1-(2,6-dichloro-3-fluorophenyl)ethyl)amino)-4-methylphthalazin-1(2H)-one	white solid, yield: 24.3%	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.64 (d, <i>J</i> = 8.8 Hz, 1H), 7.35 (s, 1H), 7.23 (d, <i>J</i> = 2.6 Hz, 1H), 7.18 – 7.08 (m, 2H), 5.48 (q, <i>J</i> = 7.0 Hz, 1H), 2.44 (s, 3H), 1.71 (d, <i>J</i> = 7.0 Hz, 3H).	366.2 Note: SFC CHIRALPA K AD - 3 250mm × 20 mm, 5 μ m Modifier: Hex(0.1%D EA):EtOH= 70:30 Rt=5.05 min
Example 239A Method 2 single unknown stereoisomer	 (S)-7-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-4-methylphthalazin-1(2H)-one	Yellow solid, yield: 32.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.08 (br s, 1H), 7.70 (d, <i>J</i> = 8.6 Hz, 1H), 7.51 (d, <i>J</i> = 6.3 Hz, 1H), 7.28 – 7.16 (m, 2H), 5.00 (t, <i>J</i> = 6.6 Hz, 1H), 2.39 (s, 3H), 1.59 (d, <i>J</i> = 6.7 Hz, 3H).	355.3 Note: SFC CHIRALPA K IF 250mm × 20 mm, 5 μ m Modifier : MtBE (0.1%DEA): EtOH=90:10 Rt=2.1 min
Example 239B Method 2 single unknown stereoisomer	 rel-(R)-7-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-4-methylphthalazin-1(2H)-one	White solid, yield: 33.8%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.09 (s, 1H), 7.70 (d, <i>J</i> = 8.6 Hz, 1H), 7.52 (d, <i>J</i> = 6.3 Hz, 1H), 7.29 – 7.15 (m, 2H), 5.05 – 4.95 (m, 1H), 2.40 (s, 3H), 1.59 (d, <i>J</i> = 6.7 Hz, 3H).	355.3 Note: SFC CHIRALPA K IF 250mm × 20 mm, 5 μ m Modifier : MtBE (0.1%DEA): EtOH=90:10 Rt=1.45 min

Example 244 Method 2 Mixture of Stereoisomers	 6'-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)spiro[cyclopropane-1,3'-indolin]-2'-one	yellow solid, yield: 21.8%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.28 (s, 1H), 6.65 (d, <i>J</i> = 8.0 Hz, 1H), 6.50 (d, <i>J</i> = 5.6 Hz, 1H), 6.24 (d, <i>J</i> = 2.0 Hz, 1H), 6.15 (dd, <i>J</i> = 8.0, 2.0 Hz, 1H), 4.79 - 4.58 (m, 1H), 1.52 (d, <i>J</i> = 6.8 Hz, 3H), 1.39 - 1.27 (m, 4H).	354.1/356.1
Example 254 Method 2 Mixture of Stereoisomers	 4-chloro-7-[1-(4,5-dichlorothiazol-2-yl)propylamino]-2H-phthalazin-1-one	White solid, yield: 8.9%	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.86 (d, <i>J</i> = 8.6 Hz, 1H), 7.37 - 7.31 (m, 2H), 4.75 (m, 1H), 2.18 - 2.03 (m, 2H), 1.11 (t, <i>J</i> = 7.4 Hz, 3H).	389.31

Preparation of N-(3-fluoro-2-methylphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide (158)

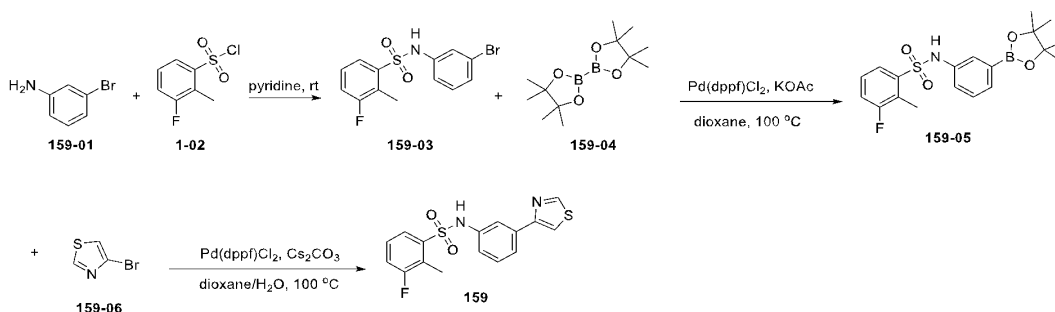


- 5 To a solution of **158-01** (150 mg, 0.604 mmol) in DCM (10 mL) was added **158-02** (126 mg, 0.604 mmol), Pyridine (143 mg, 1.81 mmol) and Triphenylphosphine (242 mg, 0.925 mmol). The mixture was stirred at 25 °C for 2 hours. The mixture was concentrated in vacuo. Purification by prep-HPLC gave the compound **158** (30 mg, 9.68 %) as a white solid. Mass (m/z): 318.3 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.27 (s, 1H), 7.92 (s, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 2.4 Hz, 1H), 7.55 (d, *J* = 5.6, 8.0 Hz, 1H), 7.42 (dd, *J* = 1.2, 9.6 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.18 (dd, *J* = 2.4, 8.0 Hz, 1H) 3.35 (dd, *J* = 6.4, 2.8 Hz, 2H), 2.81
- 10

(t, $J = 6.4$ Hz, 2H), 2.24 (d, $J = 1.6$ Hz, 3H).

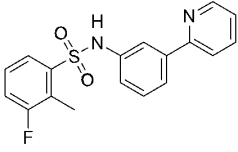
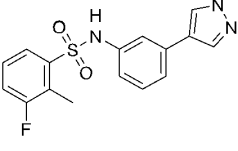
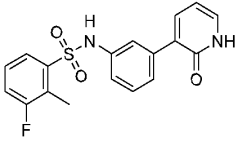
Preparation of 3-fluoro-2-methyl-N-(3-(thiazol-4-yl)phenyl)benzenesulfonamide (159)

Method 3



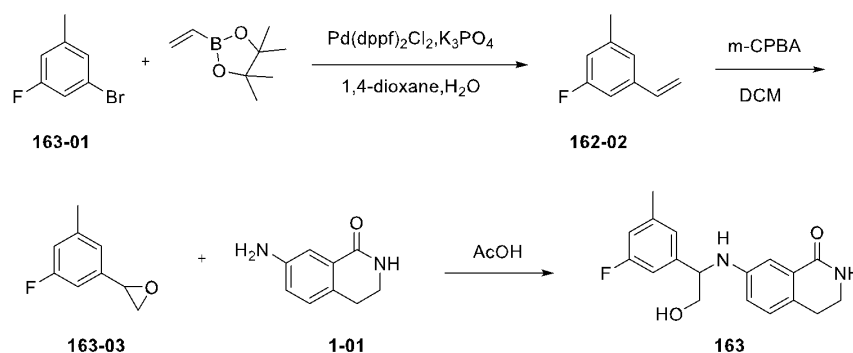
- 5 **Step 1:** To a solution of 3-bromoaniline **159-01** (5.00 g, 29.4 mmol) in pyridine (100 mL) was added 3-fluoro-2-methylbenzene-1-sulfonyl chloride **1-02** (7.30 g, 35.2 mmol) at room temperature. The mixture was stirred for 3 h at rt. The mixture was diluted with EtOAc, and washed with water. The organic layer was separated, dried over (Na₂SO₄), and concentrated under vacuum to give the desired product **159-03**. MS (m/z): 344.0 [M+H]⁺.
- 10 **Step 2:** To a solution of **159-03** (5.00 g, 14.5 mmol) in dioxane (100 mL) were added 4,4',4'',5,5'-hexamethyl-2,2'-bi(1,3,2-dioxaborolane) -**159-04** (7.40 g, 29.1 mmol), Pd(dppf)Cl₂ (1.10 g, 1.5 mmol) and KOAc (4.30 g, 43.5 mmol) at rt under N₂. The mixture was stirred for 3 h at 100 °C under N₂. The mixture was diluted with EtOAc and washed with water. The organic layer was separated, dried over (Na₂SO₄), and concentrated under vacuum.
- 15 Purification by silica gel chromatography gave the desired product **159-05**. MS (m/z): 392.1 [M+H]⁺.
- Step 3:** To a suspension of **159-05** (619 mg, 14.5 mmol) in dioxane (20 mL) and H₂O (5 mL) was added 4-bromothiazole **159-06** (200 mg, 1.21 mmol), Cs₂CO₃ (786 mg, 2.21 mmol) and Pd(dppf)Cl₂ (88 mg, 0.12 mmol) at rt under N₂. The mixture was stirred for 2 h at 100 °C under
- 20 N₂. The mixture was diluted with EtOAc, and washed with water. The organic layer was separated, dried (Na₂SO₄), and concentrated under vacuum. Purification by *prep*-HPLC gave the titled compound **159** (164.3 mg, 38.7%) as a white solid. MS (m/z): 348.9 [M+H]⁺. ¹H NMR (400 MHz, Methanol-*d*₄) δ 9.01 (d, $J = 2.0$ Hz, 1H), 7.81-7.76 (m, 2H), 7.66 (d, $J = 2.0$ Hz, 1H), 7.58 (d, $J = 8.0$ Hz, 1H), 7.28-7.24 (m, 3H), 7.07 (d, $J = 6.4$ Hz, 1H), 2.54 (d, $J = 2.0$
- 25 Hz, 3H).

Compounds **160-162** were synthesized using a method like that used in Example **159**.

Example (Compound No.) Method	Structure and Name	Appearance and Yield	¹ H NMR Data	MS (m/z) [M+H] ⁺
Example 160 Method 3	 3-fluoro-2-methyl-N-(3-(pyridin-2-yl)phenyl)benzenesulfonamide	white solid, yield: 27.0%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.65 (d, <i>J</i> = 4.4 Hz, 1H), 7.87-7.76 (m, 4H), 7.66 (d, <i>J</i> = 8.0 Hz, 1H), 7.43-7.30 (m, 4H), 7.13 (d, <i>J</i> = 7.6 Hz, 1H), 2.50 (s, 3H).	343.0
Example 161 Method 3	 3-fluoro-2-methyl-N-(3-(1-methyl-1H-pyrazol-4-yl)phenyl)benzenesulfonamide	white solid, yield: 61.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.97 (s, 1H), 7.80-7.78 (m, 1H), 7.65 (s, 1H), 7.40-7.37 (m, 2H), 7.15-7.09 (m, 3H), 6.82 (dd, <i>J</i> = 5.6, 1.6 Hz, 1H), 3.84 (s, 3H), 2.48 (d, <i>J</i> = 2.4 Hz, 3H).	346.0
Example 162 Method 3	 3-fluoro-2-methyl-N-[3-(2-oxo-1,2-dihydropyridin-3-yl)phenyl]benzenesulfonamide	white solid, yield: 4.9%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.72 (d, <i>J</i> = 7.6 Hz, 1H), 7.39 (dd, <i>J</i> = 2.0, 6.4 Hz, 1H), 7.33-7.21 (m, 4H), 7.07 (d, <i>J</i> = 8.0 Hz, 1H), 7.01 (t, <i>J</i> = 8.0 Hz, 1H), 6.84 (d, <i>J</i> = 7.6 Hz, 1H), 6.24 (t, <i>J</i> = 6.4 Hz, 1H), 6.06 (brs, 1H), 2.48 (s, 3H).	359.1

Preparation of

7-((1-(3-fluoro-5-methylphenyl)-2-hydroxyethyl)amino)-3,4-dihydroisoquinolin-1(2H)-one (163)



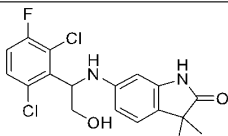
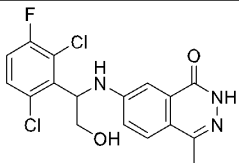
Step 1: A suspension of 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (509 mg, 2.12 mmol) and 1-bromo-3-fluoro-5-methylbenzene **163-01** (1.00 g, 5.29 mmol) in 1,4-Dioxane (20 mL) / Water (4 mL) was prepared and argon was bubbled for 10 minutes. Pd(dppf)₂Cl₂ (193 mg, 0.265 mmol) and K₃PO₄ (3.36 g, 15.9 mmol) were added. The mixture was heated to 100 °C for 16 hrs under argon. The reaction was concentrated to dryness and the residue was taken up in EtOAc (20 mL x 2) and the organics washed with 2 x 20 mL water then 20 mL of saturated brine solution. The organics were then separated and dried (MgSO₄) before concentration to dryness. The crude was then purified by flash column chromatography eluting 10% EtOAc in PE. The desired fractions were concentrated to dryness in vacuo to afford 1-fluoro-3-methyl-5-vinylbenzene **163-02** (530 mg, 3.81 mmol, 72.1% yield) as a white oil.

Step 2: To a solution of **163-02** (150 mg, 1.10 mmol) in DCM (10 mL) was added 3-chlorobenzenecarboxoperoxoic acid (190 mg, 1.10 mmol). The reaction was stirred overnight at 25 °C. The mixture was extracted by DCM (10 mL x 3). The combined organic layers were washed with NaHSO₃ a.q. (10 mL x 3), dried over Na₂SO₄ and concentrated to give the crude product, which was purified by silica gel chromatography (EA/PE = 1: 5) to give the desired product 2-(3-fluoro-5-methyl-phenyl) oxirane **163-03** (103 mg, 0.51 mmol, 46.1% yield) as a yellow oil. MS (m/z): 153.2 [M+H]⁺.

Step 3: To a solution of **163-03** (100 mg, 0.657 mmol) in Acetic acid (5mL) was added 7-amino-3,4-dihydro-2H-isoquinolin-1-one **1-01** (107 mg, 0.657 mmol). The solution was stirred at room temperature for 12 h. The mixture was extracted by DCM (25 mL x 3). The combined organic layers were washed with brine (15 mL x 3), dried over Na₂SO₄ and concentrated, which was purified by prep-HPLC to give the desired product 7-[[1-(3-fluoro-5-methyl-phenyl)-2-hydroxy-ethyl]amino]-3,4-dihydro-2H-isoquinolin-1-one **163** (15 mg, 0.0466 mmol, 7.0% yield) as a

yellow solid. MS (m/z): 315.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.73 (d, *J* = 2.8 Hz, 1H), 7.04 (s, 1H), 7.00 (d, *J* = 2.4 Hz, 1H), 6.98 – 6.90 (m, 2H), 6.84 (d, *J* = 9.7, 1H), 6.66 (dd, *J* = 8.0, 2.4 Hz, 1H), 6.25 (d, *J* = 6.4 Hz, 1H), 5.14 (s, 1H), 4.33 (q, *J* = 6.0 Hz, 1H), 3.62 – 3.50 (m, 2H), 3.25 (t, *J* = 6.8, 2H), 2.66 (t, *J* = 6.8 Hz, 2H), 2.28 (s, 3H).

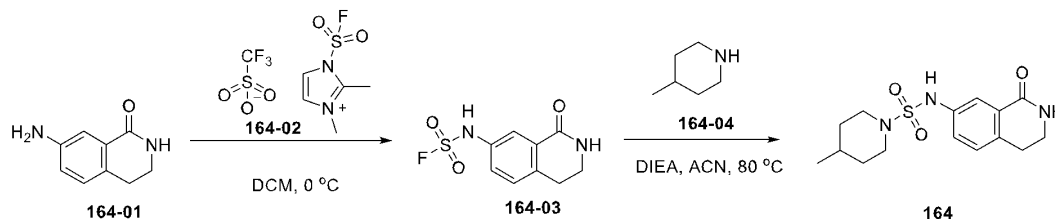
5 Compounds **238** and **250** were synthesized using a method like that used in Example **163**.

Example No.	Structure and Name	Appearance and Yield	¹ H NMR Data	MS (m/z) [M+H] ⁺
Example 238 Mixture of Stereoisomers	 6-((1-(2,6-dichloro-3-fluorophenyl)-2-hydroxyethyl)amino)-3,3-dimethylindolin-2-one	Yellow solid, yield: 35.8%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.06 (br s, 1H), 7.52 (br s, 1H), 7.36 (t, <i>J</i> = 8.4 Hz, 1H), 6.86 (d, <i>J</i> = 8.0 Hz, 1H), 6.20 – 6.08 (m, 2H), 6.01 (dd, <i>J</i> = 8.1, 2.1 Hz, 1H), 5.16 (d, <i>J</i> = 7.4 Hz, 1H), 5.06 (t, <i>J</i> = 6.0 Hz, 1H), 3.97 – 3.80 (m, 2H), 1.11 (d, <i>J</i> = 3.8 Hz, 6H).	383.2
Example 250 Mixture of Stereoisomers	 7-[[1-(2,6-dichloro-3-fluoro-phenyl)-2-hydroxy-ethyl]amino]-4-methyl-2H-phthalazin-1-one	White solid, yield: 41.3%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.94 (s, 1H), 7.61 (d, <i>J</i> = 9.0 Hz, 1H), 7.38 (t, <i>J</i> = 8.5 Hz, 1H), 7.29 (d, <i>J</i> = 7.1 Hz, 1H), 7.13 (d, <i>J</i> = 8.7 Hz, 2H), 5.37 – 5.29 (m, 1H), 4.05 – 3.95 (m, 1H), 3.93 – 3.85 (m, 1H), 3.13 – 3.07 (m, 2H), 2.34 (s, 3H).	382.3

Preparation of

4-methyl-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)piperidine-1-sulfonamide (**164**)

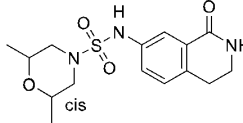
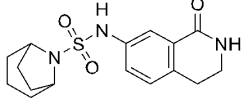
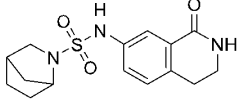
Method 4

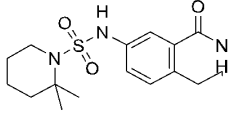
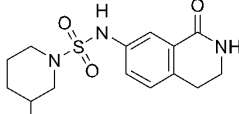
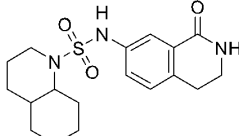


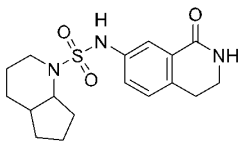
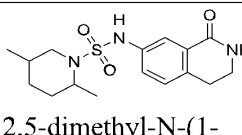
- Step 1:** A mixture solution of 7-amino-3,4-dihydroisoquinolin-1(2H)-one **164-01** (3 g, 0.019 mol), 1-(fluorosulfonyl)-2,3-dimethyl-1H-imidazol-3-ium trifluoromethanesulfonate **164-02** (6.073 g, 0.019 mol) and DCM (30 mL) was stirred at 0 °C for 16 hrs. After filtration, the filtrate was concentrated and the residue was purified through column chromatography on silica gel (EA/PE=1:1) to give the (1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)sulfamoyl fluoride **164-03** (2.5 g, 55.56% yield) as a white solid. MS (ESI) m/z 245.1 $[M+H]^+$.
- Step 2:** The mixture of (1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)sulfamoyl fluoride (90 mg, 0.37 mmol), 4-methylpiperidine **164-04** (73 mg, 0.74 mmol) and DIEA (238 mg, 1.85 mmol) in ACN (3 mL) was stirred for 16 hour at 80 °C. After reaction was completed, the solvent was removed under vacuum and the residue was purified by prep-HPLC (column-Gemini-C18 150 x 21.2 mm, 5 μ m; Mobile phase: ACN-H₂O (0.1%FA), 30%-50%) to afford the desired product **164** (7.7 mg) as a white solid. MS (ESI) m/z 324.1 $[M+H]^+$. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.90 (s, 1H), 7.93 (s, 1H), 7.68 (d, J = 2.2 Hz, 1H), 7.25 (dt, J = 16.8, 5.4 Hz, 2H), 3.55 (d, J = 12.2 Hz, 2H), 3.35 (d, J = 3.0 Hz, 2H), 2.82 (t, J = 6.6 Hz, 2H), 2.68 – 2.61 (m, 2H), 1.58 (d, J = 10.6 Hz, 2H), 1.36 (s, 1H), 0.95 (dt, J = 12.0, 8.6 Hz, 2H), 0.82 (d, J = 6.6 Hz, 3H).

Compounds **165-172** were synthesized using a method like that used in Example **164**.

Example No. Method	Structure and Name	Appearance and Yield	¹ H NMR Data	MS (m/z) $[M+H]^+$

Example 165 Method 4	 2,6-dimethyl-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)morpholine-4-sulfonamide	White solid, Yield: 6.4%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.03 (s, 1H), 7.95 (s, 1H), 7.69 (d, <i>J</i> = 2.2 Hz, 1H), 7.31 – 7.23 (m, 2H), 3.42 (d, <i>J</i> = 11.0 Hz, 4H), 3.34 (s, 2H), 2.83 (t, <i>J</i> = 6.4 Hz, 2H), 2.33 (s, 2H), 1.04 (d, <i>J</i> = 6.0 Hz, 6H).	340.2
Example 166 Method 4	 N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)-8-azabicyclo[3.2.1]octane-8-sulfonamide	White solid, Yield: 5.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.92 (s, 1H), 7.92 (s, 1H), 7.71 (d, <i>J</i> = 2.2 Hz, 1H), 7.28 – 7.21 (m, 2H), 4.01 (s, 2H), 3.33 (td, <i>J</i> = 6.8, 2.6 Hz, 2H), 2.82 (t, <i>J</i> = 6.6 Hz, 2H), 1.82 – 1.75 (m, 2H), 1.64 – 1.39 (m, 8H).	336.1
Example 167 Method 4 Mixture of Stereoisomers	 N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-azabicyclo[2.2.1]heptane-2-sulfonamide	White solid, Yield: 6.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.87 (s, 1H), 7.93 (s, 1H), 7.69 (d, <i>J</i> = 2.2 Hz, 1H), 7.27 – 7.21 (m, 2H), 3.99 (s, 1H), 3.33 (td, <i>J</i> = 6.6, 2.8 Hz, 2H), 3.11 (d, <i>J</i> = 8.4 Hz, 1H), 2.84 – 2.80 (m, 3H), 1.54 (s, 3H), 1.31 (dt, <i>J</i> = 14.6, 7.6 Hz, 4H).	322.1

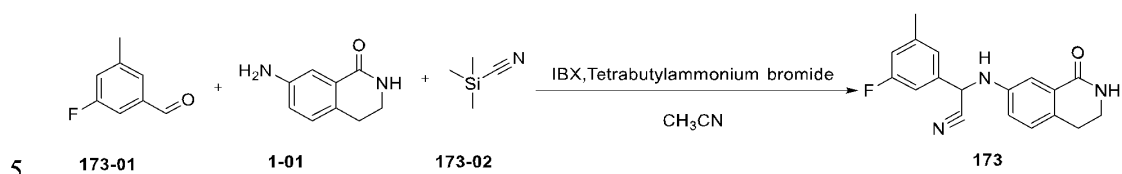
Example 168 Method 4	 2,2-dimethyl-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)piperidine-1-sulfonamide	White solid, Yield: 5.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.84 (s, 1H), 7.90 (s, 1H), 7.61 (d, <i>J</i> = 2.2 Hz, 1H), 7.23 – 7.12 (m, 2H), 3.33 (m, 4H), 2.82 (t, <i>J</i> = 6.8 Hz, 2H), 1.49 – 1.20 (m, 12H).	338.0
Example 169 Method 4 Mixture of Stereoisomers	 3-methyl-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)piperidine-1-sulfonamide	White solid, Yield: 6.7%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.89 (s, 1H), 7.90 (s, 1H), 7.64 (d, <i>J</i> = 2.2 Hz, 1H), 7.23 – 7.17 (m, 2H), 3.45 – 3.40 (m, 2H), 3.28 (dd, <i>J</i> = 6.8, 2.8 Hz, 2H), 2.78 (t, <i>J</i> = 6.6 Hz, 2H), 2.56 (dd, <i>J</i> = 12.0, 2.6 Hz, 1H), 2.27 (d, <i>J</i> = 11.8 Hz, 1H), 1.59 – 1.25 (m, 4H), 0.90 (dd, <i>J</i> = 18.8, 7.4 Hz, 1H), 0.76 (d, <i>J</i> = 6.8 Hz, 3H).	324.1
Example 170 Method 4 Mixture of Stereoisomers	 N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)octahydroquinoline-1(2H)-sulfonamide	White solid, Yield: 4.8%	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.80 (d, <i>J</i> = 2.5 Hz, 1H), 7.37 (dd, <i>J</i> = 8.2, 2.4 Hz, 1H), 7.18 (d, <i>J</i> = 8.2 Hz, 1H), 6.42 (s, 1H), 4.05 (dd, <i>J</i> = 13.1, 1.8 Hz, 1H), 3.57 (t, <i>J</i> = 6.1 Hz, 2H), 2.96 (t, <i>J</i> = 6.6 Hz, 2H), 2.94 – 2.84 (m, 1H), 2.76 (ddd, <i>J</i> = 11.6, 10.2, 3.6 Hz, 1H), 2.39 – 2.28 (m, 1H), 1.79 – 1.58 (m, 7H), 1.53 – 1.44 (m, 1H),	364.2

			1.25 – 1.18 (m, 2H), 1.14 – 0.89 (m, 2H).	
Example 171 Method 4 Mixture of Stereoisomers	 N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)octahydro-1H-cyclopenta[b]pyridine-1-sulfonamide	White solid, Yield: 3.9%	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.81 (d, <i>J</i> = 2.4 Hz, 1H), 7.39 (dd, <i>J</i> = 8.2, 2.4 Hz, 1H), 7.17 (d, <i>J</i> = 8.2 Hz, 1H), 6.39 (s, 1H), 4.19 – 4.07 (m, 1H), 3.67 – 3.50 (m, 3H), 3.04 – 2.80 (m, 3H), 1.91 – 1.86 (m, 1H), 1.77 – 1.45 (m, 7H), 1.37 – 1.24 (m, 2H), 1.12 (qd, <i>J</i> = 13.0, 3.6 Hz, 1H).	350.1
Example 172 Method 4 Mixture of Stereoisomers	 2,5-dimethyl-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)piperidine-1-sulfonamide	White solid, Yield: 7.4%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.90 (s, 1H), 7.92 (s, 1H), 7.63 (t, <i>J</i> = 2.2 Hz, 1H), 7.25 – 7.13 (m, 2H), 4.00 – 3.91 (m, 1H), 3.39 (d, <i>J</i> = 3.8 Hz, 0.35H), 3.33 (m, 2H), 3.17 (m, 0.45H), 3.02 (d, <i>J</i> = 12.6 Hz, 0.42H), 2.82 (m, <i>J</i> = 8.6, 4.2 Hz, 2H), 2.54 (d, <i>J</i> = 12.8 Hz, 0.46H), 1.75 (m, 1.21H), 1.42 (t, <i>J</i> = 12.4	338.0

			Hz, 1.79H), 1.26 – 1.02 (m, 5.06H), 0.79 (d, $J = 6.4$ Hz, 1.80H), 0.62 (d, $J = 6.8$ Hz, 1.20H).	
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Preparation of

2-(3-fluoro-5-methylphenyl)-2-((1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)amino)acetonitrile (**173**)



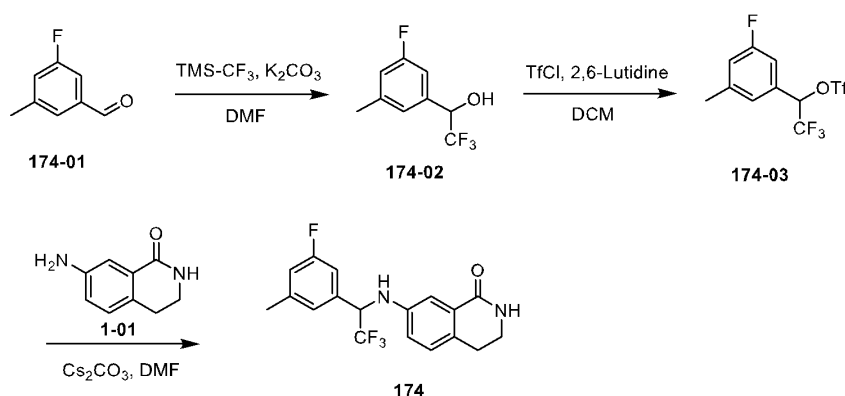
To a solution of 3-Fluoro-5-methylbenzaldehyde **173-01** (100 mg, 0.72 mmol) and 7-amino-3,4-dihydro-2H-isoquinolin-1-one **1-01** (117 mg, 0.724 mmol) and trimethylsilyl cyanide **173-02** (79 mg, 0.796 mmol) in MeCN (10 mL), tetrabutylammonium bromide (257 mg, 0.80 mmol) and IBX (223 mg, 0.80 mmol) were added. The mixture was stirred at room temperature for 16 h. The mixture was extracted by EA (25 mL x 3). The combined organic layers were washed with brine (35 mL x 3), dried over Na₂SO₄ and concentrated to give the crude product, which was purified by prep HPLC to give the desired product 2-(3-fluoro-5-methyl-phenyl)-2-[(1-oxo-3,4-dihydro-2H-isoquinolin-7-yl)amino]acetonitrile **173** (14 mg, 0.043 mmol, 6.0% yield) as a white solid. MS (m/z): 357.3 [M+H]⁺, ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.85 (d, $J = 2.8$ Hz, 1H), 7.34 (d, $J = 2.4$ Hz, 1H), 7.28 (s, 1H), 7.19 (d, $J = 9.6$, 1H), 7.15 – 7.08 (m, 2H), 6.94 (dd, $J = 8.0, 2.8$ Hz, 1H), 6.78 (d, $J = 9.6$ Hz, 1H), 6.04 (d, $J = 9.6$ Hz, 1H), 3.30 (d, $J = 2.8$ Hz, 2H), 2.77 (t, $J = 6.4$ Hz, 2H), 2.37 (s, 3H).

15

Preparation of

7-((2,2,2-trifluoro-1-(3-fluoro-5-methylphenyl)ethyl)amino)-3,4-dihydroisoquinolin-1(2H)-one (**174**)

20



Step 1: To a solution of **174-01** (200 mg, 1.45 mmol) and TMS-CF₃ (618 mg, 4.34 mmol) in DMF (5mL) was added potassium carbonate (20 mg, 0.145 mmol) and the reaction mixture was stirred at 25 °C overnight. The reaction progress was monitored by TLC. Once completed, water (10 mL) was added to the mixture slowly to quench the reaction. The reaction mixture was extracted with DCM, dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by silica column chromatograph (PE: EA=10:1) to give the product (292 mg, 97%).

¹H NMR (400 MHz, Chloroform-*d*) δ 7.05 (qd, *J* = 1.7, 0.9 Hz, 1H), 7.02 – 6.95 (m, 1H), 6.91 (dddd, *J* = 9.5, 2.4, 1.6, 0.8 Hz, 1H), 4.94 (q, *J* = 6.7 Hz, 1H), 3.37 (bs, 1H).

Step 2: To a solution of **174-02** (250 mg, 1.20 mmol) in DCM (5 mL) were added 2,6-dimethylpyridine (0.42 mL, 2.40 mmol) and trifluoromethylsulfonic anhydride (0.12 mL, 1.80 mmol) at 0 °C. Then the reaction mixture was stirred at 25 °C for 2h. The reaction progress was monitored by TLC. The SM disappeared and a new spot was found. The solvent was removed under reduced pressure and the crude was used directly in the next step.

Step 3: To a solution of **174-03** (408 mg, 1.20 mmol) in DMF (5 mL) were added **1-01** (584 mg, 3.60 mmol) and cesium carbonate (1.17 g, 3.60 mmol). Then the reaction mixture was stirred at 25 °C weekends.

The reaction progress was monitored by LC/MS. Desired mass was found with a tiny peak.

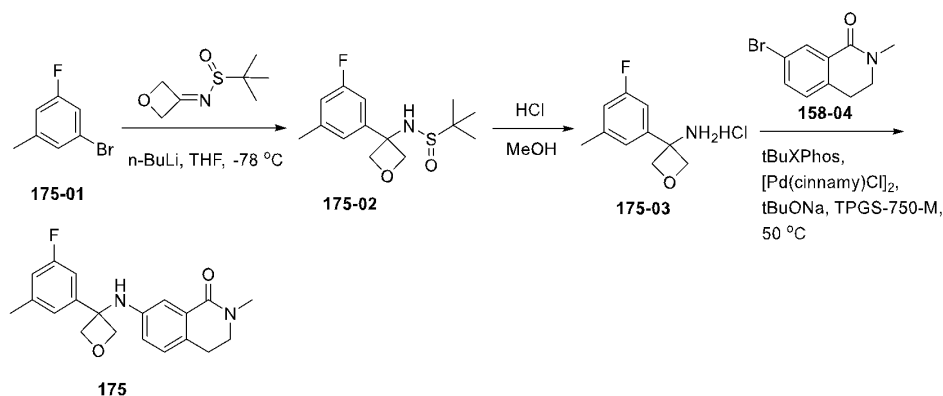
The mixture was diluted with water and extracted with EA. The organic layer was dried and concentrated under reduced pressure. The residue was purified by prep-HPLC to yield the product **174** (1 mg, 0.2%). MS (*m/z*): 353.02 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.78 (s, 1H), 7.34 (d, *J* = 2.4 Hz, 1H), 7.31 – 7.27 (m, 2H), 7.04 – 7.01 (m, 2H), 6.95 (dd, *J* =

8.4, 2.4 Hz, 1H), 6.73 (d, $J = 10.4$ Hz, 1H), 5.74 – 5.44 (m, 1H), 3.28 – 3.26 (m, 2H), 2.70 (t, $J = 6.4$ Hz, 2H), 2.30 (m, 2H).

Preparation of

7-((3-(3-fluoro-5-methylphenyl)oxetan-3-yl)amino)-2-methyl-3,4-dihydroisoquinolin-

5 1(2H)-one (175)



Step 1: To a solution of **175-01** (500 mg, 2.65 mmol) in THF (15 mL) was added n-BuLi (2.4 M in hexanes, 1.2 mL, 2.91 mmol) at -70°C and the reaction mixture was stirred for 20 min. Then 2-methyl-N-(oxetan-3-ylidene)propane-2-sulfinamide (5.00 eq, 2.3 g, 13.2 mmol) was added at -70°C and the mixture was allowed to warm to rt and stirred for another 2 h. The reaction progress was monitored by LC/MS. The desired mass was found in main peak. The reaction mixture was diluted with water (50 mL) and extracted with DCM (100 mL, 2 times). The organic layer was separated, dried (MgSO_4) and concentrated under reduced pressure. The residue was purified by silica column chromatograph (PE: EA=5:1) to give the product **175-02** (480 mg, 64%). MS (m/z) 286.24 $[\text{M}+\text{H}]^+$

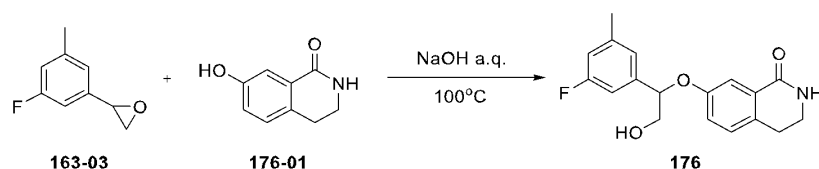
Step 2: To a solution of **175-02** (220 mg, 0.77 mmol) in methanol (1.5 mL) was added HCl (4M in dioxane, 0.35 mL, 1.16 mmol) at 0°C and the reaction mixture was stirred for 10 min. The reaction progress was monitored by LC/MS. The product was identified. Then the solvent was removed and the obtained solid was washed with MTBE, dried to yield the product (52 mg, 37%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.31 (s, 2H), 7.32 – 7.18 (m, 2H), 7.17 – 7.05 (m, 1H), 4.97 (d, $J = 7.5$ Hz, 2H), 4.88 (d, $J = 7.5$ Hz, 2H), 2.37 (s, 3H).

Step 3: To a mixture of **175-03** (5.7 mg, 0.0316 mmol) and **175-04** (7.6 mg, 0.0316 mmol) were added *t*-BuONa (9.1 mg, 0.0948 mmol), tBuXPhos (1.3 mg, 0.0032 mmol), $[\text{Pd}(\text{cinnamyl})\text{Cl}]_2$ (0.82 mg, 0.0016 mmol) and TPGS-750-M (1.0 mL). Then the mixture was

stirred at 50 °C overnight. The reaction progress was monitored by LC-MS. Desired mass was found. Then the reaction mixture was diluted with water (10 mL), extracted with DCM (15 mL, 2 times). The organic layer was separated, dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by prep-HPLC to yield the product **175** (5 mg, 46%). MS (m/z) 315.29 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.34 (s, 1H), 7.10 – 7.04 (m, 2H), 6.96 – 6.90 (m, 2H), 6.80 (d, *J* = 2.4 Hz, 1H), 6.26 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.83 (d, *J* = 6.0 Hz, 2H), 4.75 (d, *J* = 6.0 Hz, 2H), 3.43 (t, *J* = 6.4 Hz, 2H), 2.95 (s, 3H), 2.75 (t, *J* = 6.4 Hz, 2H), 2.33 (s, 3H).

Preparation of

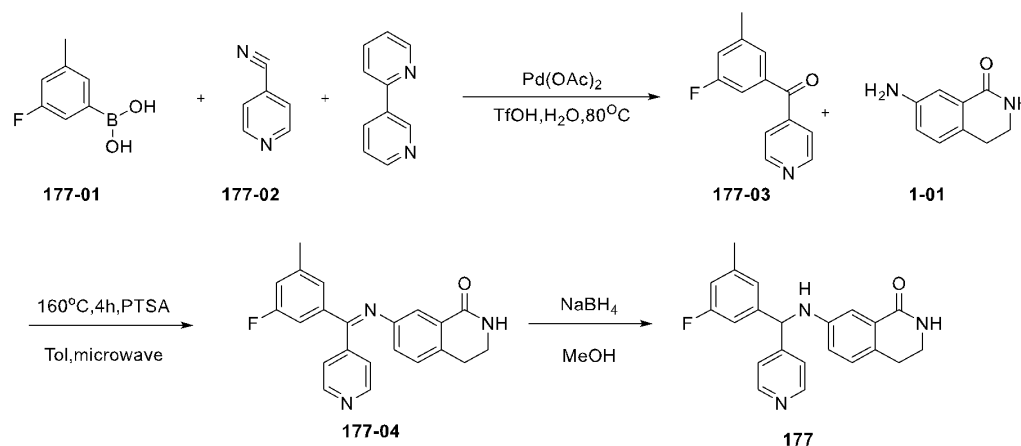
10 7-(1-(3-fluoro-5-methylphenyl)-2-hydroxyethoxy)-3,4-dihydroisoquinolin-1(2H)-one (**176**)



Step 1: To a solution of 2-(3-fluoro-5-methyl-phenyl)oxirane **163-03** (100 mg, 0.657 mmol) in NaOH a.q. (5 mL) was added 7-hydroxy-3,4-dihydro-2H-isoquinolin-1-one **176-01** (107 mg, 0.66 mmol). The reaction was stirred overnight at 100 °C. The mixture was extracted by EA (10 mL x 3). The combined organic layers were washed with brine (10 mL x 3), dried over Na₂SO₄ and concentrated to give the crude product, which was purified by prep-HPLC to give the desired product 7-[1-(3-fluoro-5-methyl-phenyl)-2-hydroxy-ethoxy]-3,4-dihydro-2H-isoquinolin-1-one **176** (11 mg, 0.034 mmol, 5.1% yield) as a white solid. MS (m/z): 316.3 [M+H]⁺, ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.90 (d, *J* = 2.8 Hz, 1H), 7.32 (d, *J* = 2.8 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.08 – 7.02 (m, 2H), 7.00 (d, *J* = 9.6, 1H), 6.92 (d, *J* = 10.0 Hz, 1H), 5.30 – 5.25 (m, 1H), 5.14 (t, *J* = 6.0 Hz, 1H), 3.77 – 3.55 (m, 2H), 3.31 – 3.27 (m, 2H), 2.77 (t, *J* = 6.5 Hz, 2H), 2.29 (s, 3H).

Preparation of

25 7-(((3-fluoro-5-methylphenyl)(pyridin-4-yl)methyl)amino)-3,4-dihydroisoquinolin-1(2H)-one (**177**) Method 5



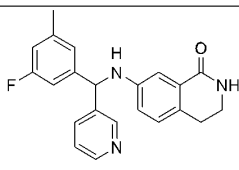
- Step 1:** To a solution of (3-fluoro-5-methyl-phenyl)boronic acid **177-01** (532 mg, 3.46 mmol) and pyridine-4-carbonitrile **177-02** (300 mg, 2.88 mmol) in Water (9 mL) and TfOH (3 mL) were added 2-(2-pyridyl)pyridine (23 mg, 0.144 mmol) and Pd(OAc)₂ (32 mg, 0.144 mmol).
- 5 The mixture was stirred at 80 °C for 16 h. The mixture was extracted by EA (25 mL x 3). The combined organic layers were washed with brine (15 mL x 3), dried over Na₂SO₄ and concentrated to give the crude product, which was purified by TLC (MeOH/DCM = 1/25) to give the desired product (3-fluoro-5-methyl-phenyl)-(4-pyridyl)methanone **177-03** (285 mg, 1.26 mmol, 43.6% yield) as a yellow oil. MS (m/z): 216.2 [M+H]⁺.
- 10 **Step 2:** A solution of **177-03** (50 mg, 0.23 mmol), 7-amino-3,4-dihydro-2H-isoquinolin-1-one **1-01** (38 mg, 0.23 mmol), p-Toluenesulfonic acid (4.0 mg, 0.023 mmol) in Toluene (5 mL) was stirred at 160 °C under microwave for 5 h. The reaction was filtered and concentrated under vacuum to afford the desired product 7-[(E)-[(3-fluoro-5-methyl-phenyl)-(4-pyridyl)methylene]amino]-3,4-dihydro-2H-isoquinolin-1-one **177-04** (45 mg, 0.075 mmol,
- 15 32.34% yield) as yellow oil. MS (m/z): 360.3 [M+H]⁺.

Step 3: To a solution of **177-04** (45 mg, 0.125 mmol) in Methanol (5 mL) was added NaBH₄ (9.5 mg, 0.25 mmol). The solution was stirred at 25 °C for 1 h. The reaction was quenched with water (10 mL), and extracted by DCM (15 mL x 3). The combined organic layers were washed with brine (15 mL x 3), dried over sodium sulfate and concentrated to give the crude product,

20 which was purified by prep-HPLC to give the desired product 7-[[[(3-fluoro-5-methyl-phenyl)-(4-pyridyl)methyl]amino]-3,4-dihydro-2H-isoquinolin-1-one **177** (6.0 mg, 0.016 mmol, 13.1% yield) as a white solid. MS (m/z): 362.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.51 (d, *J* = 5.2 Hz, 2H), 7.74 (d, *J* = 2.8 Hz, 1H), 7.47 – 7.41 (m, 2H), 7.18 (d, *J* = 2.8 Hz, 1H),

7.13 (s, 1H), 7.10 (d, $J = 9.8$ Hz, 1H), 6.98 (d, $J = 8.0$ Hz, 1H), 6.91 (d, $J = 9.6$, 1H), 6.81 (dd, $J = 8.2, 2.6$ Hz, 1H), 6.64 (d, $J = 8.0$ Hz, 1H), 5.73 (d, $J = 7.6$ Hz, 1H), 3.28 – 3.25 (m, 2H), 2.69 (t, $J = 6.8$ Hz, 2H), 2.28 (s, 3H).

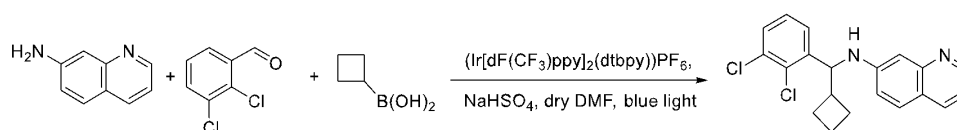
Compound 178 was synthesized using a method similar to that used for Compound 177.

Example No. Method	Structure and Name	Appearance and Yield	¹ H NMR Data	MS (m/z) [M+H] ⁺
Example 178 Method 5 Mixture of Stereoisomers	 7-(((3-fluoro-5-methylphenyl)(pyridin-3-yl)methyl)amino)-3,4-dihydroisoquinolin-1(2H)-one	White solid, Yield: 14.57 %	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.67 (s, 1H), 8.46 (s, 1H), 7.81 (d, $J = 8.0$ Hz, 1H), 7.74 (d, $J = 2.8$ Hz, 1H), 7.42 - 7.35 (m, 1H), 7.19 (d, $J = 2.8$ Hz, 1H), 7.13 (s, 1H), 7.09 (d, $J = 9.8$, 1H), 6.99 (d, $J = 8.0$ Hz, 1H), 6.90 (d, $J = 9.6$, 1H), 6.82 (dd, $J = 8.2, 2.6$ Hz, 1H), 6.63 (d, $J = 7.6$ Hz, 1H), 5.78 (d, $J = 7.2$ Hz, 1H), 3.29 - 3.23 (m, 2H), 2.69 (t, $J = 6.4$ Hz, 2H), 2.28 (s, 3H).	362.1

5

Preparation of

N-(cyclobutyl(2,3-dichlorophenyl)methyl)quinolin-7-amine (179)

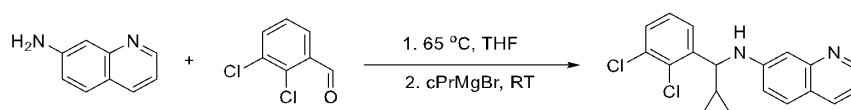


A mixture of quinolin-7-amine (1.00 eq, 150 mg, 1.04 mmol), (Ir[dF(CF₃)ppy]₂(dtbpy))PF₆ (0.0500 eq, 58 mg, 0.0520 mmol) cyclobutylboronic acid (2.00 eq, 208 mg, 2.08 mmol), NaHSO₄ (0.200 eq, 25 mg, 0.208 mmol) and 2,3-dichlorobenzaldehyde (1.00 eq, 182 mg, 1.04 mmol) in dry DMF (10mL) was stirred for 2 days at 45 °C under blue light under nitrogen. The reaction mixture was diluted with water and extracted with ethyl acetate twice. The combined organic layers were washed with water and brine, dried over sodium sulfate and concentrated under vacuum. The residue was purified by Prep-TLC (dichloromethane/methanol 10/1) and then

purified by Prep-HPLC to afford N-[cyclobutyl-(2,3-dichlorophenyl)methyl]quinolin-7-amine (13 mg, 0.0353 mmol, 3.3 % yield) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.55 (dd, $J = 4.3, 1.8$ Hz, 1H), 7.98 (dd, $J = 8.0, 1.8$ Hz, 1H), 7.60 (d, $J = 8.9$ Hz, 1H), 7.53 – 7.42 (m, 2H), 7.30 (t, $J = 7.8$ Hz, 1H), 7.19 – 7.11 (m, 1H), 7.07 (dd, $J = 8.0, 4.3$ Hz, 1H), 6.94 (d, $J = 7.4$ Hz, 1H), 6.55 (d, $J = 2.3$ Hz, 1H), 4.92 (t, $J = 8.1$ Hz, 1H), 2.78 – 2.66 (m, 1H), 2.17 – 2.06 (m, 1H), 2.02 – 1.90 (m, 2H), 1.86 – 1.79 (m, 2H), 1.78 – 1.70 (m, 1H).

Preparation of

N-(cyclopropyl(2,3-dichlorophenyl)methyl)quinolin-7-amine (180)

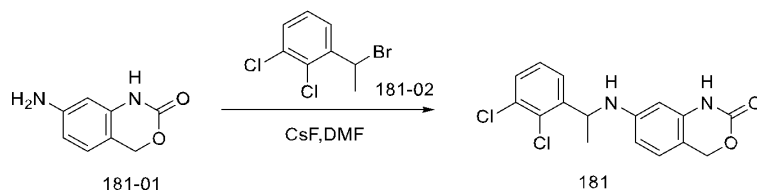


A mixture of quinolin-7-amine (1.00 eq, 144 mg, 0.999 mmol) and 2,3-dichlorobenzaldehyde (1.00 eq, 175 mg, 0.999 mmol) in THF (10 mL) was stirred for 2 h at 65 °C. The reaction mixture was cooled before bromo(cyclopropyl)magnesium (0.5 M in THF) (3.00 eq, 6.0 mL, 3.00 mmol) was added. The reaction was stirred overnight at RT and then quenched with water. The resulting mixture was extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. The residue was purified by Prep-TLC (dichloromethane/methanol 15/1) and then Prep-HPLC to afford N-[cyclopropyl-(2,3-dichlorophenyl)methyl]quinolin-7-amine (19 mg, 0.0548 mmol, 5.4 % yield) as a yellow solid. LCMS (ESI, m/z) 343.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.53 (dd, $J = 4.3, 1.8$ Hz, 1H), 7.98 (dd, $J = 8.0, 1.8$ Hz, 1H), 7.60 (d, $J = 8.9$ Hz, 1H), 7.57 – 7.49 (m, 2H), 7.32 (t, $J = 7.9$ Hz, 1H), 7.22 (d, $J = 6.9$ Hz, 1H), 7.15 (dd, $J = 8.9, 2.4$ Hz, 1H), 7.07 (dd, $J = 8.0, 4.3$ Hz, 1H), 6.44 (d, $J = 2.2$ Hz, 1H), 4.48 (t, $J = 7.5$ Hz, 1H), 1.33 – 1.23 (m, 1H), 0.68 – 0.56 (m, 1H), 0.56 – 0.45 (m, 2H), 0.41 – 0.29 (m, 1H).

Preparation of

7-((1-(2,3-dichlorophenyl)ethyl)amino)-1,4-dihydro-2H-benzo[d][1,3]oxazin-2-one (181)

Method 6

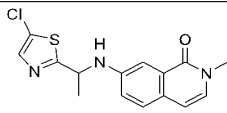


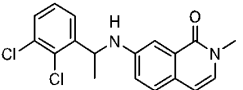
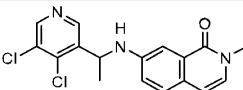
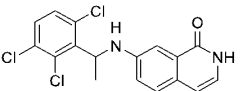
181-1 (100 mg, 0.61 mmol), **181-02** (307 mg, 1.22 mmol) and CsF (185 mg, 1.21 mmol) were dissolved in DMF (5 mL) and stirred at 30°C for 4 h. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by Pre-HPLC gave the titled compound **181** (4.7 mg, 2.3%) as a light green solid. MS (m/z): 337.0 (M+H⁺), ¹H NMR (400 MHz, Methanol-*d*₄) δ 10.71 (s, 1H), 8.31 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.19 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.11 (t, *J* = 7.8 Hz, 1H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.43 (d, *J* = 7.0 Hz, 1H), 6.86 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.79 (d, *J* = 2.2 Hz, 1H), 5.84 (s, 2H), 5.55 (p, *J* = 6.8 Hz, 1H), 2.22 (d, *J* = 6.6 Hz, 3H).

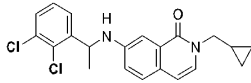
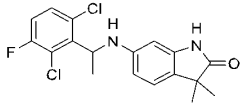
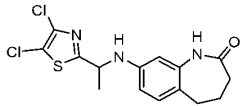
Compounds 182-186, 215, 229-231, 233-234A, 236, 245-246, 249, 257-263, 266-267, 271, 275, 277-278, 282, 288, 302-302C, 310-311, 314-316, 318, 321-322, 324-325, 330, 342, 349, 350-354, 382-388 were synthesized using a method like that used for Compound **181**.

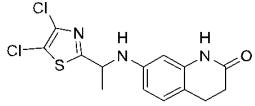
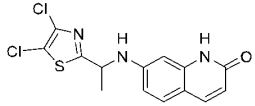
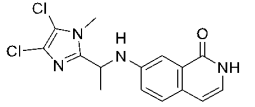
Some other substitution conditions were also used according to different substrate:

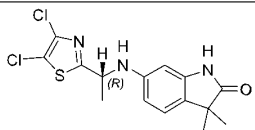
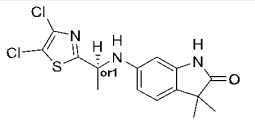
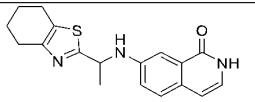
2) DMF, H₂O (1/1), KI, CaCO₃; 3) DMF, KI, CaCO₃; or 4) DMF, KI, CsCO₃

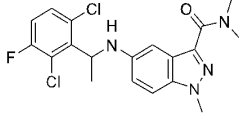
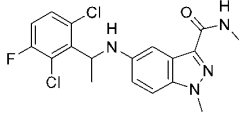
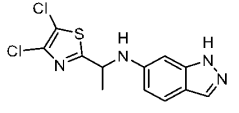
Example No. Method	Structure and Name	Appearance and Yield	¹ H NMR Data	MS (m/z) [M+H] ⁺
Example 182 Method 6 Mixture of Stereoisomers	 7-((1-(5-chlorothiazol-2-yl)ethyl)amino)-2-methylisoquinolin-1(2H)-one	Yellow solid, yield: 29.0%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.75 (s, 1H), 7.42 (d, <i>J</i> = 8.6 Hz, 1H), 7.23 (d, <i>J</i> = 2.6 Hz, 1H), 7.16 (d, <i>J</i> = 7.2 Hz, 1H), 7.11 (dd, <i>J</i> = 8.6, 2.6 Hz, 1H), 6.91 (d, <i>J</i> = 6.0 Hz, 1H), 6.43 (d, <i>J</i> = 7.2 Hz, 1H), 4.81 (p, <i>J</i> = 6.6 Hz, 1H), 3.43 (s, 3H), 1.57 (d, <i>J</i> = 6.8 Hz, 3H).	320

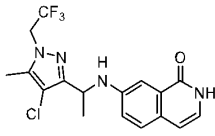
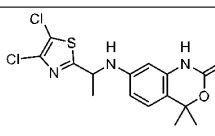
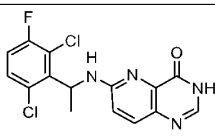
Example 183 Method 6 Mixture of Stereoisomers	 7-((1-(2,3-dichlorophenyl)ethyl)amino)-2-methylisoquinolin-1(2H)-one	white solid, yield: 42.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.50 (dd, <i>J</i> = 7.6, 1.6 Hz, 1H), 7.41 (dd, <i>J</i> = 7.8, 1.6 Hz, 1H), 7.35 (d, <i>J</i> = 9.0 Hz, 1H), 7.28 (t, <i>J</i> = 7.8 Hz, 1H), 7.10 (d, <i>J</i> = 7.2 Hz, 1H), 7.02 – 6.97 (m, 2H), 6.91 (d, <i>J</i> = 7.0 Hz, 1H), 6.37 (d, <i>J</i> = 7.2 Hz, 1H), 4.90 (p, <i>J</i> = 6.8 Hz, 1H), 3.40 (s, 3H), 1.46 (d, <i>J</i> = 6.8 Hz, 3H).	347.3
Example 184 Method 6 Mixture of Stereoisomers	 7-((1-(4,5-dichloropyridin-3-yl)ethyl)amino)-2-methylisoquinolin-1(2H)-one	white solid, yield: 32.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.64 (s, 1H), 8.52 (s, 1H), 7.38 (d, <i>J</i> = 8.8 Hz, 1H), 7.12 (d, <i>J</i> = 7.2 Hz, 1H), 7.06 - 7.01 (m, 2H), 6.94 (d, <i>J</i> = 7.2 Hz, 1H), 6.39 (d, <i>J</i> = 7.3 Hz, 1H), 4.93 (p, <i>J</i> = 6.7 Hz, 1H), 3.40 (s, 3H), 1.53 (d, <i>J</i> = 6.7 Hz, 3H).	348.3
Example 185 Method 6 Mixture of Stereoisomers	 7-((1-(2,3,6-trichlorophenyl)ethyl)amino)isoquinolin-1(2H)-one	yellow solid, yield: 6.7%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.81 (d, <i>J</i> = 5.6 Hz, 1H), 7.54 (d, <i>J</i> = 8.2 Hz, 1H), 7.33 (d, <i>J</i> = 8.6 Hz, 1H), 7.08 (d, <i>J</i> = 2.5 Hz, 1H), 7.00 (dd, <i>J</i> = 8.6, 2.6 Hz, 1H), 6.82-6.74 (m, 2H), 6.29 (d, <i>J</i> = 7.0 Hz, 1H), 5.42 – 5.27 (m, 1H), 1.61 (d, <i>J</i> = 6.9 Hz, 3H).	367

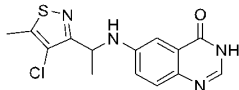
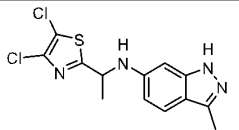
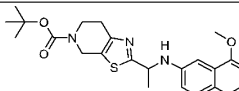
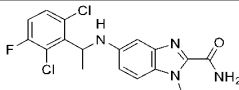
Example 186 Method 6 Mixture of Stereoisomers	 2-(2,3-dichlorophenyl)-7-((1-(2,3-dichlorophenyl)ethyl)amino)isoquinolin-1(2H)-one	white solid, yield: 45.3%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.50 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.42 (dd, <i>J</i> = 7.8, 1.6 Hz, 1H), 7.36 (d, <i>J</i> = 8.4 Hz, 1H), 7.29 (t, <i>J</i> = 7.8 Hz, 1H), 7.14 (d, <i>J</i> = 7.2 Hz, 1H), 7.04 – 6.98 (m, 2H), 6.91 (d, <i>J</i> = 7.0 Hz, 1H), 6.39 (d, <i>J</i> = 7.2 Hz, 1H), 4.91 (p, <i>J</i> = 6.6 Hz, 1H), 3.72 (dd, <i>J</i> = 7.2, 3.8 Hz, 2H), 1.47 (d, <i>J</i> = 6.6 Hz, 3H), 1.24 – 1.12 (m, 1H), 0.46 – 0.39 (m, 2H), 0.37 – 0.31 (m, 2H).	387.1
Example 215 Method 6 Mixture of Stereoisomers	 6-[1-(2,6-dichloro-3-fluorophenyl)ethylamino]-3,3-dimethyl-indolin-2-one	red solid, yield: 41.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.06 (s, 1H), 7.44 (s, 1H), 7.33 (t, <i>J</i> = 8.6 Hz, 1H), 6.84 (d, <i>J</i> = 8.0 Hz, 1H), 6.31 (d, <i>J</i> = 7.8 Hz, 1H), 6.09 (d, <i>J</i> = 2.1 Hz, 1H), 5.96 (dd, <i>J</i> = 8.1, 2.1 Hz, 1H), 5.19 – 5.10 (m, 1H), 1.55 (d, <i>J</i> = 7.0 Hz, 3H), 1.11 (s, 3H), 1.10 (s, 3H).	367.07
Example 229 Method 6 Mixture of Stereoisomers	 8-[1-(4,5-dichlorothiazol-2-yl)ethylamino]-1,3,4,5-tetrahydro-1-benzazepin-2-one	white solid, yield: 30.4%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.34 (s, 1H), 6.95 (d, <i>J</i> = 8.2 Hz, 1H), 6.51 (d, <i>J</i> = 5.5 Hz, 1H), 6.32 (dd, <i>J</i> = 8.1, 2.4 Hz, 1H), 6.25 (d, <i>J</i> = 2.4 Hz, 1H), 4.67 – 4.59 (m, 1H), 2.55 – 2.51 (m, 2H),	356.03

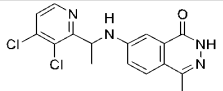
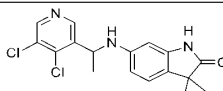
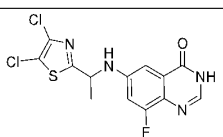
			2.15 – 2.06 (m, 2H), 2.05 – 1.94 (m, 2H), 1.51 (d, $J = 6.8$ Hz, 3H).	
Example 230 Method 6 Mixture of Stereoisomers	 7-[1-(4,5-dichlorothiazol-2-yl)ethylamino]-3,4-dihydro-1H-quinolin-2-one	White solid, yield: 23.7%	^1H NMR (400 MHz, DMSO- d_6) δ 9.86 (s, 1H), 6.87 (d, $J = 8.0$ Hz, 1H), 6.48 (d, $J = 5.5$ Hz, 1H), 6.21 – 6.13 (m, 2H), 4.63 – 4.55 (m, 1H), 2.69 (t, $J = 8.5$, 6.5 Hz, 2H), 2.36 (t, $J = 8.5$, 6.5 Hz, 2H), 1.50 (d, $J = 6.8$ Hz, 3H).	341.92
Example 231 Method 6 Mixture of Stereoisomers	 7-[1-(4,5-dichlorothiazol-2-yl)ethylamino]-1H-quinolin-2-one	White solid, yield: 27.8%	^1H NMR (400 MHz, DMSO- d_6) δ 11.29 (s, 1H), 7.64 (dd, $J = 9.4$, 1.9 Hz, 1H), 7.35 (dd, $J = 8.6$, 1.9 Hz, 1H), 7.17 (dd, $J = 5.9$, 1.9 Hz, 1H), 6.59 – 6.53 (m, 1H), 6.37 (d, $J = 2.2$ Hz, 1H), 6.10 (d, $J = 10.1$, 2.5 Hz, 1H), 4.81 – 4.71 (m, 1H), 1.56 (dd, $J = 6.8$, 1.9 Hz, 3H).	339.92
Example 233 Method 6 Mixture of Stereoisomers	 7-((1-(4,5-dichloro-1-methyl-1H-imidazol-2-yl)ethyl)amino)isoquinolin-1(2H)-one	White solid, yield: 34.7%	^1H NMR (400 MHz, DMSO- d_6) δ 10.94 (d, $J = 5.0$ Hz, 1H), 7.39 (d, $J = 8.6$ Hz, 1H), 7.27 (d, $J = 2.1$ Hz, 1H), 7.09 (dd, $J = 8.6$, 2.4 Hz, 1H), 6.90 – 6.78 (m, 1H), 6.49 (d, $J = 8.2$ Hz, 1H), 6.36 (d, $J = 7.0$ Hz, 1H), 4.94 – 4.86 (m, 1H), 3.60 (s,	336.8

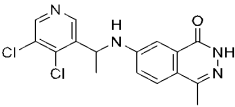
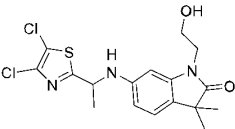
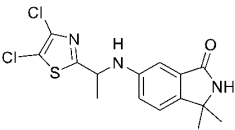
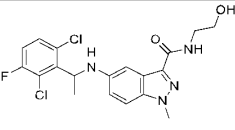
			3H), 1.48 (d, $J = 6.6$ Hz, 3H).	
Example 234 Method 6 single unknown stereoisomer	 6-[[[(1R)-1-(4,5-dichlorothiazol-2-yl)ethyl]amino]-3,3-dimethyl-indolin-2-one	White solid, yield: 32.4%	^1H NMR (400 MHz, DMSO- d_6) δ 10.05 (s, 1H), 6.93 (d, $J = 8.0$ Hz, 1H), 6.50 (d, $J = 5.2$ Hz, 1H), 6.25 – 6.09 (m, 2H), 4.70 – 4.54 (m, 1H), 1.50 (d, $J = 6.6$ Hz, 3H), 1.14 (s, 6H).	356.26 CHIRAL Cellulose SB, 2cm $\times$ 25cm, 5 μ m, Mobile Phase A: Hex, Mobile Phase B: EtOH Flow Rate: 20mL/min 220nm, 25°C Rt: 8.22min.
Example 234A Method 6 single unknown stereoisomer	 6-[[[(1S)-1-(4,5-dichlorothiazol-2-yl)ethyl]amino]-3,3-dimethyl-indolin-2-one	White solid, yield: 33.8%	^1H NMR (400 MHz, DMSO- d_6) δ 10.06 (s, 1H), 6.94 (d, $J = 8.0$ Hz, 1H), 6.50 (d, $J = 5.3$ Hz, 1H), 6.16 (d, $J = 6.1$ Hz, 2H), 4.76 – 4.54 (m, 1H), 1.51 (d, $J = 6.8$ Hz, 3H), 1.15 (s, 6H).	356.26 CHIRAL Cellulose SB, 2cm $\times$ 25cm, 5 μ m, Mobile Phase A: Hex, Mobile Phase B: EtOH Flow Rate: 20mL/min 220nm, 25°C Rt: 7.13 min.
Example 236 Method 6 Mixture of	 7-((1-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)amino)-3,3-dimethyl-indolin-2-one	White solid, yield: 12.1%	^1H NMR (400 MHz, CDCl $_3$) δ 10.03 (s, 1H), 7.54 (d, $J = 1.2$ Hz, 1H), 7.39 (d, $J = 8.4$ Hz, 1H), 7.06 (dd, $J =$	326.0

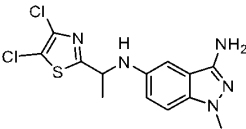
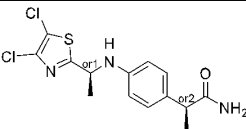
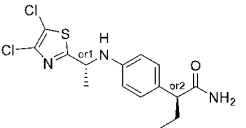
Stereoisomers	yl)ethyl)amino)isoquinolin-1(2H)-one		8.8, 2.8 Hz, 1H), 6.90 (s, 1H), 6.45 (d, $J = 7.2$ Hz, 1H), 4.97-5.02 (m, 1H), 2.79 (s, 2H), 2.69 (s, 2H), 1.93 – 1.77 (m, 4H), 1.71 (d, $J = 6.8$ Hz, 3H).	
Example 245 Method 6 Mixture of Stereoisomers	 5-((1-(2,6-dichloro-3-fluorophenyl)ethyl)amino)-N,N,1-trimethyl-1H-indazole-3-carboxamide	white solid, yield: 24.8%	^1H NMR (400 MHz, DMSO- d_6) δ 7.57 – 7.26 (m, 1H), 7.40 (d, $J = 9.0$ Hz, 1H), 7.31 (t, $J = 8.6$ Hz, 1H), 6.96 (dd, $J = 9.0, 2.2$ Hz, 1H), 6.69 (d, $J = 2.1$ Hz, 1H), 6.29 (d, $J = 8.3$ Hz, 1H), 5.26 (p, $J = 7.1$ Hz, 1H), 3.95 (s, 3H), 3.16 (s, 3H), 3.00 (s, 3H), 1.61 (d, $J = 7.0$ Hz, 3H).	219.6
Example 246 Method 6 Mixture of Stereoisomers	 5-((1-(2,6-dichloro-3-fluorophenyl)ethyl)amino)-N,1-dimethyl-1H-indazole-3-carboxamide	White solid, yield: 3.10%	^1H NMR (400 MHz, DMSO- d_6) δ 7.95 (q, $J = 4.7$ Hz, 1H), 7.57 – 7.41 (m, 1H), 7.40 (d, $J = 9.0$ Hz, 1H), 7.30 (t, $J = 8.6$ Hz, 1H), 7.01 – 6.91 (m, 2H), 6.30 (d, $J = 8.3$ Hz, 1H), 5.28 (p, $J = 7.2$ Hz, 1H), 3.96 (s, 3H), 2.74 (d, $J = 4.6$ Hz, 3H), 1.61 (d, $J = 6.9$ Hz, 3H).	395.2
Example 249 Method 6 Mixture of Stereoisomers	 N-(1-(4,5-dichlorothiazol-2-yl)ethyl)-1H-indazole-6-amine	Off-white solid, yield: 20.0%	^1H NMR (400 MHz, DMSO- d_6) δ 7.78 (s, 1H), 7.46 (d, $J = 8.7$ Hz, 1H), 6.76 (s, 1H), 6.64 (dd, $J = 8.6, 1.9$ Hz, 1H), 6.35 (s, 1H), 4.76 (q, $J = 6.6$ Hz,	313

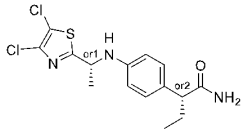
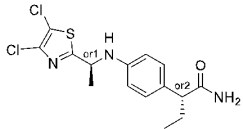
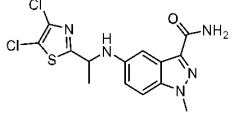
			1H), 1.56 (d, J = 6.7 Hz, 3H).	
Example 257 Method 6 Mixture of Stereoisomers	 7-((1-(4-chloro-5-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-3-yl)ethyl)amino)isoquinolin-1(2H)-one	white solid, yield: 9.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.84 (d, J = 5.6 Hz, 1H), 7.31 (d, J = 8.6 Hz, 1H), 7.24 (d, J = 2.5 Hz, 1H), 7.06 (dd, J = 8.6, 2.6 Hz, 1H), 6.80 (dd, J = 7.0, 5.7 Hz, 1H), 6.38 (d, J = 7.6 Hz, 1H), 6.32 (d, J = 7.0 Hz, 1H), 5.12-4.99 (m, 2H), 4.66 (p, J = 6.9 Hz, 1H), 2.23 (s, 3H), 1.50 (d, J = 6.8 Hz, 3H).	385.1
Example 258 Method 6 Mixture of Stereoisomers	 7-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-4,4-dimethyl-1,4-dihydro-2H-benzo[d][1,3]oxazin-2-one	white solid, yield: 15.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.93 (s, 1H), 6.96 (d, J = 8.3 Hz, 1H), 6.70 (d, J = 5.4 Hz, 1H), 6.25 (dd, J = 8.4, 2.3 Hz, 1H), 6.13 (d, J = 2.2 Hz, 1H), 4.62 (p, J = 6.6 Hz, 1H), 1.57 – 1.38 (m, 9H).	372.2
Example 259 Method 6 Mixture of Stereoisomers	 6-((1-(2,6-dichloro-3-fluorophenyl)ethyl)amino)pyrido[3,2-d]pyrimidin-4(3H)-one	White solid, yield: 21.3%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.77 (s, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.37 (dd, J = 8.8, 4.9 Hz, 1H), 7.25 (t, J = 8.6 Hz, 1H), 7.04 (d, J = 9.0 Hz, 1H), 5.77 (q, J = 7.3 Hz, 1H), 1.56 (d, J = 7.3 Hz, 3H).	353.1

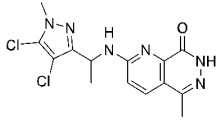
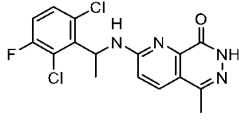
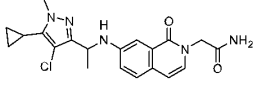
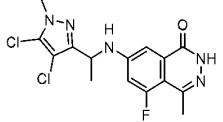
Example 260 Method 6 Mixture of Stereoisomers	 6-((1-(4-chloro-5-methylisothiazol-3-yl)ethyl)amino)quinazolin-4(3H)-one	White solid, yield: 55%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.86 (s, 1H), 7.76 (d, <i>J</i> = 3.4 Hz, 1H), 7.39 (d, <i>J</i> = 8.8 Hz, 1H), 7.16 (dd, <i>J</i> = 8.8, 2.8 Hz, 1H), 7.02 (d, <i>J</i> = 2.8 Hz, 1H), 6.75 (d, <i>J</i> = 7.9 Hz, 1H), 4.87 – 4.82 (m, 1H), 2.47 (s, 3H), 1.52 (d, <i>J</i> = 6.7 Hz, 3H).	321.3
Example 261 Method 6 Mixture of Stereoisomers	 N-(1-(4,5-dichlorothiazol-2-yl)ethyl)-3-methyl-1H-indazol-6-amine	white solid, yield: 3.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.95 (s, 1H), 7.39 (d, <i>J</i> = 8.6 Hz, 1H), 6.71 (d, <i>J</i> = 5.4 Hz, 1H), 6.59 (dd, <i>J</i> = 8.7, 1.9 Hz, 1H), 6.28 (d, <i>J</i> = 1.8 Hz, 1H), 4.75 (q, <i>J</i> = 6.9, 5.5 Hz, 1H), 2.34 (s, 3H), 1.56 (d, <i>J</i> = 6.7 Hz, 3H).	327
Example 262 Method 6 Mixture of Stereoisomers	 tert-butyl 2-(1-((1-methoxyisoquinolin-7-yl)amino)ethyl)-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate	white solid, yield: 15.9%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.67 (d, <i>J</i> = 5.7 Hz, 1H), 7.62 (d, <i>J</i> = 8.9 Hz, 1H), 7.24 (dd, <i>J</i> = 8.8, 2.4 Hz, 1H), 7.14 (d, <i>J</i> = 5.7 Hz, 1H), 7.00 (d, <i>J</i> = 2.4 Hz, 1H), 6.96 (d, <i>J</i> = 6.5 Hz, 1H), 4.86 (p, <i>J</i> = 6.6 Hz, 1H), 4.48 (s, 2H), 3.95 (s, 3H), 3.63 (s, 2H), 2.79 – 2.71 (m, 2H), 1.57 (d, <i>J</i> = 6.7 Hz, 3H), 1.39 (s, 9H).	441
Example 263 Method 6	 5-((1-(2,6-dichloro-3-fluorophenyl)ethyl)amino)-1-methyl-1H-indazol-6-amine	yellow solid, yield: 17.3%	¹ H NMR (400 MHz, CDCl ₃) δ 7.45 (s, 1H), 7.19 (d, <i>J</i> = 9.2 Hz, 1H), 6.97 – 6.89 (m, 1H),	382.9

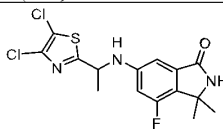
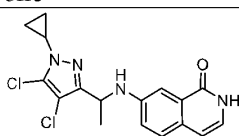
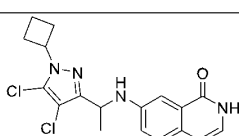
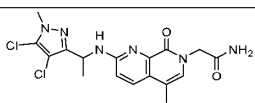
Mixture of Stereoisomers	fluorophenyl)ethyl)amino)-1-methyl-1H-benzo[d]imidazole-2-carboxamide		6.85 – 6.78 (m, 2H), 5.47 (s, 2H), 4.78 (s, 1H), 4.10 (s, 3H), 2.01 (s, 1H), 1.69 (d, $J = 7.2$ Hz, 3H).	
Example 266 Method 6 Mixture of Stereoisomers	 7-((1-(3,4-dichloropyridin-2-yl)ethyl)amino)-4-methylphthalazin-1(2H)-one	white solid, yield: 24.8%	^1H NMR (400 MHz, DMSO- d_6) δ 11.98 (s, 1H), 8.46 (d, $J = 5.0$ Hz, 1H), 7.66 (d, $J = 5.0$ Hz, 1H), 7.60 (d, $J = 8.8$ Hz, 1H), 7.32 (d, $J = 8.2$ Hz, 1H), 7.17 (d, $J = 8.8$ Hz, 1H), 7.11 (s, 1H), 5.21 (dd, $J = 14.2, 6.9$ Hz, 1H), 2.36 (s, 3H), 1.52 (d, $J = 6.6$ Hz, 3H).	349.0
Example 267 Method 6 Mixture of Stereoisomers	 6-((1-(4,5-dichloropyridin-3-yl)ethyl)amino)-3,3-dimethylindolin-2-one	yellow solid, yield: 28.1%	^1H NMR (400 MHz, DMSO- d_6) δ 10.02 (s, 1H), 8.64 (s, 1H), 8.53 (s, 1H), 6.88 (d, $J = 8.0$ Hz, 1H), 6.50 (d, $J = 6.8$ Hz, 1H), 6.02 (s, 1H), 5.97 (dd, $J = 8.0, 1.9$ Hz, 1H), 4.81 – 4.74 (m, 1H), 1.47 (d, $J = 6.8$ Hz, 3H), 1.12 (s, 3H), 1.11 (s, 3H)	349.9
Example 271 Method 6 Mixture of Stereoisomers	 6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-8-fluoroquinazolin-4(3H)-one	White solid, yield: 65.6%	^1H NMR (400 MHz, DMSO- d_6) δ 12.13 (s, 1H), 7.85 (s, 1H), 7.23 (d, $J = 6.3$ Hz, 1H), 7.08 (dd, $J = 12.8, 2.5$ Hz, 1H), 6.95 (d, $J = 2.5$ Hz, 1H), 4.93 (t, $J = 6.7$ Hz, 1H), 1.56 (d, $J = 6.7$ Hz, 3H).	359.2

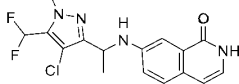
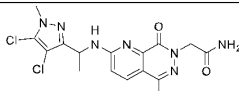
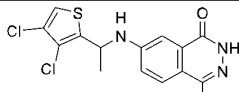
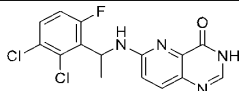
Example 275 Method 6 Mixture of Stereoisomers	 7-((1-(4,5-dichloropyridin-3-yl)ethyl)amino)-4-methylphthalazin-1(2H)-one	yellow solid, yield: 11.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.02 (s, 1H), 8.67 (s, 1H), 8.53 (s, 1H), 7.65 (d, <i>J</i> = 8.8 Hz, 1H), 7.49 (d, <i>J</i> = 7.2 Hz, 1H), 7.12 (dd, <i>J</i> = 8.8, 2.2 Hz, 1H), 7.02 (s, 1H), 5.00 (t, <i>J</i> = 6.8 Hz, 1H), 2.36 (s, 3H), 1.56 (d, <i>J</i> = 6.8 Hz, 3H).	349.1
Example 277 Method 6 Mixture of Stereoisomers	 6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-1-(2-hydroxyethyl)-3,3-dimethylindolin-2-one	white solid, yield: 36.4%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.01 (d, <i>J</i> = 8.0 Hz, 1H), 6.53 (d, <i>J</i> = 6.0 Hz, 1H), 6.42 (d, <i>J</i> = 2.0 Hz, 1H), 6.19 (dd, <i>J</i> = 8.0, 2.0 Hz, 1H), 4.82 (t, <i>J</i> = 5.6 Hz, 1H), 4.76 (p, <i>J</i> = 6.4 Hz, 1H), 3.63 (t, <i>J</i> = 6.0 Hz, 2H), 3.53 (q, <i>J</i> = 5.6 Hz, 2H), 1.52 (d, <i>J</i> = 6.8 Hz, 3H), 1.18 (s, 6H).	400.0/402.0
Example 278 Method 6 Mixture of Stereoisomers	 6-[1-(4,5-dichlorothiazol-2-yl)ethylamino]-3,3-dimethyl-isoindolin-1-one	white solid, yield: 35.3%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.47 (s, 1H), 7.31 (d, <i>J</i> = 8.2 Hz, 1H), 6.87 (dd, <i>J</i> = 8.3, 2.3 Hz, 1H), 6.76 (d, <i>J</i> = 5.6 Hz, 1H), 6.70 (d, <i>J</i> = 2.2 Hz, 1H), 4.84 – 4.70 (m, 1H), 1.54 (d, <i>J</i> = 6.7 Hz, 3H), 1.36 (d, <i>J</i> = 1.6 Hz, 6H).	356.26
Example 282 Method 6 Mixture of Stereoisomers	 5-((1-(2,6-dichloro-3-fluorophenyl)ethyl)amino)-N-(2-hydroxyethyl)-1-methyl-1H-indazole-3-carboxamide	White solid, yield: 8.09%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.81 (t, <i>J</i> = 5.8 Hz, 1H), 7.41 (d, <i>J</i> = 9.0 Hz, 1H), 7.30 (t, <i>J</i> = 8.6 Hz, 1H), 7.01 – 6.91 (m, 2H), 6.32 (d, <i>J</i> = 8.2 Hz, 1H), 5.28 (p, <i>J</i> = 7.1 Hz, 1H), 4.75 (t, <i>J</i> = 5.4 Hz, 1H), 3.96 (s, 3H), 3.49 (q, <i>J</i> = 5.9 Hz, 2H), 3.37 – 3.27 (m, 2H), 1.60 (d, <i>J</i> = 7.0 Hz, 3H).	425.2

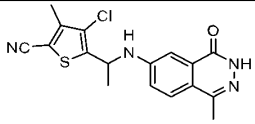
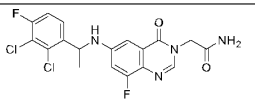
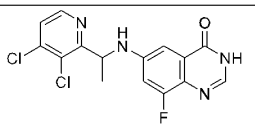
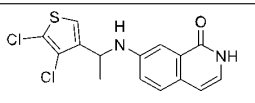
Example 288 Method 6 Mixture of Stereoisomers	 N5-(1-(4,5-dichlorothiazol-2-yl)ethyl)-1-methyl-1H-indazole-3,5-diamine	gray solid, yield: 19.3%	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.14 (d, <i>J</i> = 9.0 Hz, 1H), 7.06 (d, <i>J</i> = 9.0 Hz, 1H), 6.58 (s, 1H), 4.70 (q, <i>J</i> = 6.6 Hz, 1H), 3.74 (s, 3H), 1.70 (d, <i>J</i> = 6.5 Hz, 3H).	342
Example 302 Method 6 single unknown stereoisomer	 rel-(R)-2-(4-(((R)-1-(4,5-dichlorothiazol-2-yl)ethyl)amino)phenyl)butanamide	white solid, yield: 6.0%	NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.26 (d, <i>J</i> = 2.0 Hz, 1H), 7.01 – 6.98 (m, 2H), 6.65 (s, 1H), 6.50 – 6.47 (m, 2H), 6.37 (d, <i>J</i> = 5.6 Hz, 1H), 4.62 (m, 1H), 3.09 – 3.05 (m, 1H), 1.88 – 1.73 (m, 1H), 1.49 – 1.44 (m, 4H), 0.73 (t, <i>J</i> = 7.4 Hz, 3H).	357.9 Note: SFC Thar prep 80 CHIRALPA K WHELK-01, 250mm × 21.1 mm, 5 μ m, Modifier: 40% EtOH (NH ₄ OH 0.2%) R _t =3.64 min
Example 302A Method 6 single unknown stereoisomer	 rel-(R)-2-(4-(((S)-1-(4,5-dichlorothiazol-2-yl)ethyl)amino)phenyl)butanamide	white solid, yield: 8.39%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.26 (d, <i>J</i> = 2.0 Hz, 1H), 7.01 – 6.98 (m, 2H), 6.65 (s, 1H), 6.50 – 6.47 (m, 2H), 6.37 (d, <i>J</i> = 5.6 Hz, 1H), 4.62 (m, 1H), 3.09 – 3.05 (m, 1H), 1.88 – 1.73 (m, 1H), 1.49 – 1.44 (m, 4H), 0.73 (t, <i>J</i> = 7.4 Hz, 3H).	357.9 Note: SFC Thar prep 80 CHIRALPA K WHELK-01, 250mm × 21.1 mm, 5 μ m, Modifier: 40% EtOH (NH ₄ OH 0.2%) R _t =1.94 min
Example 302B Method 6		white solid, yield:	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.26 (d, <i>J</i>	357.9 Note: SFC Thar prep

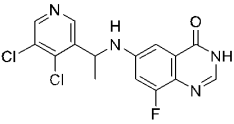
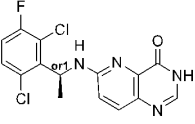
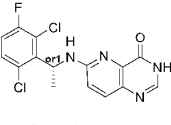
single unknown stereoisomer	 rel-(R)-2-(4-(((R)-1-(4,5-dichlorothiazol-2-yl)ethyl)amino)phenyl)butanamide	6.16%	= 2.0 Hz, 1H), 7.01 – 6.98 (m, 2H), 6.65 (s, 1H), 6.50 – 6.47 (m, 2H), 6.37 (d, $J = 5.6$ Hz, 1H), 4.62 (m, 1H), 3.09 – 3.05 (m, 1H), 1.88 – 1.73 (m, 1H), 1.49 – 1.44 (m, 4H), 0.73 (t, $J = 7.4$ Hz, 3H).	80 CHIRALPA K WHELK-01, 250mm × 21.1 mm, 5 μ m, Modifier: 40% EtOH (NH ₄ OH 0.2%) Rt=3.23 min
Example 302C Method 6 single unknown stereoisomer	 rel-(R)-2-(4-(((S)-1-(4,5-dichlorothiazol-2-yl)ethyl)amino)phenyl)butanamide	white solid, yield: 9.30%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.26 (d, $J = 2.0$ Hz, 1H), 7.01 – 6.98 (m, 2H), 6.65 (s, 1H), 6.50 – 6.47 (m, 2H), 6.37 (d, $J = 5.6$ Hz, 1H), 4.62 (m, 1H), 3.09 – 3.05 (m, 1H), 1.88 – 1.73 (m, 1H), 1.49 – 1.44 (m, 4H), 0.73 (t, $J = 7.4$ Hz, 3H).	357.9 Note: SFC Thar prep 80 CHIRALPA K WHELK-01, 250mm × 21.1 mm, 5 μ m, Modifier: 40% EtOH (NH ₄ OH 0.2%) Rt=5.34 min
Example 310 Method 6 Mixture of Stereoisomer s	 5-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-1-methyl-1H-indazole-3-carboxamide	white solid, yield: 56.8%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.51 (d, $J = 9.0$ Hz, 1H), 7.45 (s, 1H), 7.17 – 7.11 (m, 2H), 7.00 (dd, $J = 9.0, 2.2$ Hz, 1H), 6.57 (d, $J = 5.6$ Hz, 1H), 4.78 – 4.70 (m, 1H), 4.01 (s, 3H), 1.56 (d, $J = 6.7$ Hz, 3H).	370.1

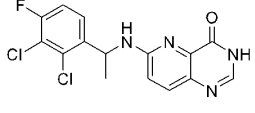
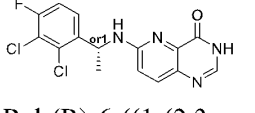
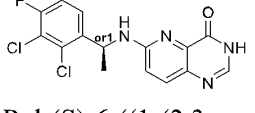
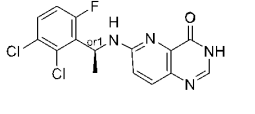
Example 311 Method 6 Mixture of Stereoisomers	 2-((1-(4,5-dichloro-1-methyl-1H-pyrazol-3-yl)ethyl)amino)-5-methylpyrido[2,3-d]pyridazin-8(7H)-one	White solid, yield: 56%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.32 (s, 1H), 8.01 (s, 1H), 7.89 (d, <i>J</i> = 7.5 Hz, 1H), 7.05 (d, <i>J</i> = 9.0 Hz, 1H), 5.51 (s, 1H), 3.81 (s, 3H), 2.37 (s, 3H), 1.50 (d, <i>J</i> = 6.8 Hz, 3H).	353.1
Example 314 Method 6 Mixture of Stereoisomers	 2-((1-(2,6-dichloro-3-fluorophenyl)ethyl)amino)-5-methylpyrido[2,3-d]pyridazin-8(7H)-one	White solid, yield: 21%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.10 (s, 1H), 8.21 (s, 1H), 7.86 (d, <i>J</i> = 9.0 Hz, 1H), 7.41 (s, 1H), 7.30 (t, <i>J</i> = 8.7 Hz, 1H), 7.04 (d, <i>J</i> = 22.5 Hz, 1H), 5.85 (s, 1H), 2.33 (s, 3H), 1.61 (d, <i>J</i> = 7.2 Hz, 3H).	367.6
Example 315 Method 6 Mixture of Stereoisomers	 2-(7-((1-(4-chloro-5-cyclopropyl-1-methyl-1H-pyrazol-3-yl)ethyl)amino)-1-oxoisoquinolin-2(1H-yl)acetamide	yellow solid, yield: 15.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.54 (s, 1H), 7.33 (d, <i>J</i> = 8.4 Hz, 1H), 7.22 (d, <i>J</i> = 2.4 Hz, 1H), 7.12 (s, 1H), 7.08 (dd, <i>J</i> = 8.8 Hz, 2.4 Hz, 1H), 7.00 (d, <i>J</i> = 7.2 Hz, 1H), 6.37-6.34 (m, 2H), 4.64-4.56 (m, 1H), 4.53-4.43 (m, 2H), 3.76 (s, 3H), 1.77-1.69 (m, 1H), 1.46 (d, <i>J</i> = 6.8 Hz, 3H), 0.98-0.92 (m, 2H), 0.82-0.77 (m, 2H).	399.9
Example 316 Method 6 Mixture of Stereoisomers	 7-((1-(4,5-dichloro-1-methyl-1H-pyrazol-3-yl)ethyl)amino)-5-methylpyrido[2,3-d]pyridazin-8(7H)-one	white solid, yield: 47.3%	¹ H NMR (400 MHz, CDCl ₃) δ 7.36 (d, <i>J</i> = 2.4 Hz, 1H), 6.76 (dd, <i>J</i> = 14.0, 2.4 Hz, 1H), 4.81-4.83 (m, 1H), 3.81 (s, 3H), 2.58 (d, <i>J</i> = 6.4 Hz, 3H), 1.60 (d, <i>J</i> = 6.8 Hz, 3H).	369.9

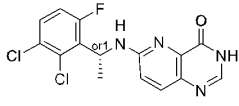
	yl)ethyl)amino)-5-fluoro-4-methylphthalazin-1(2H)-one			
Example 318 Method 6 Mixture of Stereoisomers	 6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-4-fluoro-3,3-dimethylisoindolin-1-one	white solid, yield: 10.9%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.69 (s, 1H), 7.04 (d, <i>J</i> = 6.4 Hz, 1H), 6.63 (d, <i>J</i> = 11.2 Hz, 2H), 4.85 (p, <i>J</i> = 6.8 Hz, 1H), 1.53 (d, <i>J</i> = 6.8 Hz, 3H), 1.43 (d, <i>J</i> = 1.6 Hz, 6H).	374.1/376.1
Example 321 Method 6 Mixture of Stereoisomers	 7-((1-(4,5-dichloro-1-cyclopropyl-1H-pyrazol-3-yl)ethyl)amino)isoquinolin-1(2H)-one	Off white solid, yield: 27%	¹ H NMR (400 MHz, CDCl ₃) δ 9.13 (s, 1H), 7.57 (d, <i>J</i> = 2.4 Hz, 1H), 7.36 (d, <i>J</i> = 8.8 Hz, 1H), 7.04 (dd, <i>J</i> = 8.4, 2.4 Hz, 1H), 6.86-6.83 (m, 1H), 6.41 (d, <i>J</i> = 7.2 Hz, 1H), 4.85 (t, <i>J</i> = 7.2 Hz, 1H), 4.59 (s, 1H), 3.43-3.37 (m, 1H), 1.25-1.11 (m, 3H), 1.07-1.05 (m, 2H).	363.0
Example 322 Method 6 Mixture of Stereoisomers	 7-((1-(4,5-dichloro-1-cyclobutyl-1H-pyrazol-3-yl)ethyl)amino)isoquinolin-1(2H)-one	yellow solid, yield: 15.5 %	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.86 (d, <i>J</i> = 5.6 Hz, 1H), 7.34 (d, <i>J</i> = 8.6 Hz, 1H), 7.27 (d, <i>J</i> = 2.4 Hz, 1H), 7.09 (dd, <i>J</i> = 8.6, 2.5 Hz, 1H), 6.81 (dd, <i>J</i> = 6.9, 5.8 Hz, 1H), 6.47 (d, <i>J</i> = 7.1 Hz, 1H), 6.33 (d, <i>J</i> = 6.8 Hz, 1H), 4.93-4.84 (m, 1H), 4.72-4.63 (m, 1H), 2.62-2.52 (m, 2H), 2.37-2.27 (m, 2H), 1.86-1.75 (m, 2H), 1.55 (d, <i>J</i> = 6.8 Hz, 3H).	376.9
Example 324 Method 6	 2-(2-((1-(4,5-dichloro-1H-pyrazol-3-yl)ethyl)amino)-1H-benzimidazol-5-yl)acetamide	white solid, yield:	¹ H NMR (400 MHz, CDCl ₃) δ 7.75 (d, <i>J</i> = 9.2 Hz, 1H), 7.18 (s, 1H), 6.91 (d, <i>J</i> = 9.2	408.9

Mixture of Stereoisomers	dichloro-1-methyl-1H-pyrazol-3-yl)ethyl)amino)-5-methyl-8-oxo-1,7-naphthyridin-7(8H)-yl)acetamide	39.8 %	Hz, 1H), 6.86 (s, 1H), 6.18 (s, 1H), 5.60 (s, 1H), 5.17 - 5.07 (m, 1H), 4.66 (s, 2H), 3.79 (s, 3H), 2.20 (s, 3H), 1.63 (d, $J = 6.8$ Hz, 3H).	
Example 325 Method 6 Mixture of Stereoisomers	 7-((1-(4-chloro-5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)ethyl)amino)isoquinolin-1(2H)-one	yellow solid, yield: 15.5%	^1H NMR (400 MHz, DMSO- d_6) δ 10.88 (d, $J = 5.2$ Hz, 1H), 7.39 (s, 0.25H), 7.35 (d, $J = 8.4$ Hz, 1H), 7.26 (s, 0.5H), 7.22 (d, $J = 2.4$ Hz, 1H), 7.13 (s, 0.25H), 7.07 (dd, $J = 8.8, 2.4$ Hz, 1H), 6.86-6.77 (m, 1H), 6.46 (d, $J = 7.6$ Hz, 1H), 6.34 (d, $J = 6.8$ Hz, 1H), 4.77-4.63 (m, 1H), 3.89 (s, 3H), 1.51 (d, $J = 6.8$ Hz, 3H)	342.9
Example 330 Method 6 Mixture of Stereoisomers	 2-(2-((1-(4,5-dichloro-1-methyl-1H-pyrazol-3-yl)ethyl)amino)-5-methyl-8-oxopyrido[2,3-d]pyridazin-7(8H)-yl)acetamide	White solid, yield: 23%	^1H NMR (400 MHz, DMSO- d_6) δ 8.02 (d, $J = 7.6$ Hz, 1H), 7.89 (d, $J = 9.0$ Hz, 1H), 7.46 (s, 1H), 7.13 (s, 1H), 7.02 (d, $J = 9.0$ Hz, 1H), 5.52 (s, 1H), 4.58 (s, 2H), 3.80 (s, 3H), 2.38 (s, 3H), 1.49 (d, $J = 7.0$ Hz, 3H).	410.1
Example 342 Method 6 Mixture of Stereoisomers	 7-((1-(3,4-dichlorothiophen-2-yl)ethyl)amino)-4-methylphthalazin-1(2H)-one	yellow solid, yield: 14.8%	12.04 (s, 1H), 7.68-7.65 (m, 2H), 7.44 (d, $J = 5.6$ Hz, 1H), 7.14-7.10 (m, 2H), 4.91 (t, $J = 6.4$ Hz, 1H), 2.38 (s, 3H), 1.56 (d, $J = 6.8$ Hz, 3H).	354.0
Example 349 Method 6	 7-((1-(3-chloro-4-fluorophenyl)ethyl)amino)-4-methylphthalazin-1(2H)-one	White solid, yield:	^1H NMR (400 MHz, DMSO- d_6) δ 12.11 (s, 1H), 7.82 (s, 1H), 7.73 (d, $J = 7.6$ Hz, 1H),	353.2

Mixture of Stereoisomers	6-((1-(2,3-dichloro-6-fluorophenyl)ethyl)amino)pyrido[3,2-d]pyrimidin-4(3H)-one	30.3%	7.66 (d, $J = 9.2$ Hz, 1H), 7.55 (dd, $J = 8.8$, 5.2 Hz, 1H), 7.22 (dd, $J = 10.4$, 8.8 Hz, 1H), 7.04 (d, $J = 9.2$ Hz, 1H), 5.85 – 5.66 (m, 1H), 1.57 (d, $J = 7.2$ Hz, 3H).	
Example 350 Method 6 Mixture of Stereoisomers	 4-chloro-3-methyl-5-((1-((1-methyl-4-oxo-3,4-dihydrophthalazin-6-yl)amino)ethyl)thiophene-2-carbonitrile	White solid, yield: 42.7%	^1H NMR (400 MHz, DMSO- d_6) δ 12.06 (s, 1H), 7.68 (d, $J = 8.9$ Hz, 1H), 7.14 (d, $J = 8.4$ Hz, 1H), 7.10 (s, 1H), 5.03 – 4.91 (m, 1H), 2.38 (s, 3H), 2.34 (s, 3H), 1.58 (d, $J = 6.6$ Hz, 3H)	359.1
Example 351 Method 9 Mixture of Stereoisomers	 2-(6-((1-(2,3-dichloro-4-fluorophenyl)ethyl)amino)-8-fluoro-4-oxoquinazolin-3(4H)-yl)acetamide	white solid, yield: 46.7%	^1H NMR (400 MHz, DMSO- d_6) δ 7.98 (s, 1H), 7.73 – 7.65 (m, 1H), 7.48 – 7.37 (m, 1H), 7.25 (d, $J = 6.8$ Hz, 2H), 6.92 (dd, $J = 12.8$, 2.4 Hz, 1H), 6.67 (d, $J = 2.4$ Hz, 1H), 4.86 (p, $J = 6.8$ Hz, 1H), 4.51 (s, 2H), 1.46 (d, $J = 6.8$ Hz, 3H).	427.3
Example 352 Method 6 Mixture of Stereoisomers	 6-((1-(3,4-dichloropyridin-2-yl)ethyl)amino)-8-fluoroquinazolin-4(3H)-one	White solid, yield: 45.1%	^1H NMR (400 MHz, DMSO) δ 12.04 (s, 1H), 8.47 (d, $J = 5.2$ Hz, 1H), 7.78 (s, 1H), 7.66 (d, $J = 5.2$ Hz, 1H), 7.06 – 6.97 (m, 2H), 6.82 (d, $J = 2.5$ Hz, 1H), 5.20 – 5.09 (m, 1H), 1.48 (d, $J = 6.8$ Hz, 3H).	353.1
Example 353 Method 6	 7-((1-(4,5-dichlorothiophen-2-yl)ethyl)amino)-1,2,3,4-tetrahydroquinolin-6(1H)-one	White solid, yield:	^1H NMR (400 MHz, DMSO) δ 10.91 (d, $J = 4.8$ Hz, 1H), 7.37 (d, $J = 8.5$ Hz, 1H), 7.34 (s,	339.1

Mixture of Stereoisomers	dichlorothiophen-3-yl)ethyl)amino)isoquinolin-1(2H)-one	5.8%	¹ H), 7.08 (d, <i>J</i> = 2.2 Hz, 1H), 7.03 (dd, <i>J</i> = 8.4, 2.4 Hz, 1H), 6.87 – 6.78 (m, 1H), 6.61 (d, <i>J</i> = 7.2 Hz, 1H), 6.34 (d, <i>J</i> = 6.8 Hz, 1H), 4.62 – 4.52 (m, 1H), 1.47 (d, <i>J</i> = 6.8 Hz, 3H).	
Example 354 Method 6 Mixture of Stereoisomers	 6-((1-(4,5-dichloropyridin-3-yl)ethyl)amino)-8-fluoroquinazolin-4(3H)-one	White solid, yield: 13.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.07 (s, 1H), 8.67 (s, 1H), 8.54 (s, 1H), 7.79 (d, <i>J</i> = 3.4 Hz, 1H), 7.23 (d, <i>J</i> = 7.5 Hz, 1H), 6.95 (dd, <i>J</i> = 12.6, 2.6 Hz, 1H), 6.70 (d, <i>J</i> = 2.5 Hz, 1H), 4.93 (p, <i>J</i> = 6.6 Hz, 1H), 1.53 (d, <i>J</i> = 6.8 Hz, 3H).	353.2
Example 382 Method 6 single unknown stereoisomer	 rel-(S)-6-((1-(2,6-dichloro-3-fluorophenyl)ethyl)amino)pyrido[3,2-d]pyrimidin-4(3H)-one	White solid, yield: 35.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.97 (s, 1H), 7.80 – 7.73 (m, 2H), 7.65 (d, <i>J</i> = 9.0 Hz, 1H), 7.39 (dd, <i>J</i> = 9.0, 5.1 Hz, 1H), 7.28 (t, <i>J</i> = 8.7 Hz, 1H), 7.04 (d, <i>J</i> = 8.9 Hz, 1H), 5.80 (p, <i>J</i> = 7.1 Hz, 1H), 1.59 (d, <i>J</i> = 7.3 Hz, 3H).	353.1 Note: CHIRAL Cellulose SB, 2cm*25cm, 5um, MeOH/DC M, MtBE, 20mL/min, Rt = 4.671 min
Example 383 Method 6 single unknown stereoisomer	 Rel-(R)-6-((1-(2,6-dichloro-3-fluorophenyl)ethyl)amino)pyrido[3,2-d]pyrimidin-4(3H)-one	White solid, yield: 36.7%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.97 (s, 1H), 7.80 – 7.73 (m, 2H), 7.65 (d, <i>J</i> = 9.0 Hz, 1H), 7.39 (dd, <i>J</i> = 9.0, 5.1 Hz, 1H), 7.28 (t, <i>J</i> = 8.7 Hz, 1H), 7.04 (d, <i>J</i> = 8.9 Hz, 1H), 5.80 (p, <i>J</i> = 7.1 Hz, 1H), 1.59 (d, <i>J</i> = 7.3 Hz, 3H).	353.1 Note: CHIRAL Cellulose SB, 2cm*25cm, 5um, MeOH/DC M, MtBE, 20mL/min, Rt = 3.440

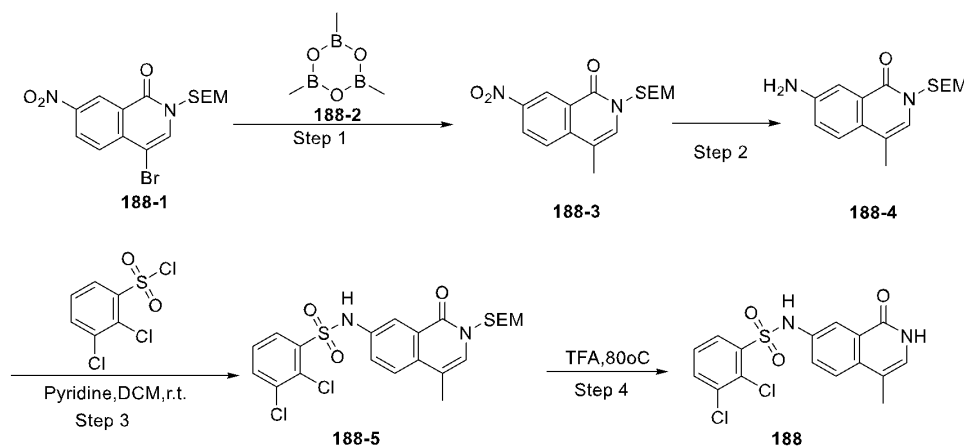
				min
Example 384 Method 6 Mixture of Stereoisomers	 6-((1-(2,3-dichloro-4-fluorophenyl)ethyl)amino)pyrido[3,2-d]pyrimidin-4(3H)-one	White solid, yield: 47.7%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.11 (s, 1H), 7.86 (d, <i>J</i> = 7.6 Hz, 1H), 7.80 (d, <i>J</i> = 3.5 Hz, 1H), 7.69 (d, <i>J</i> = 8.9 Hz, 1H), 7.51 (dd, <i>J</i> = 8.9, 5.9 Hz, 1H), 7.41 (t, <i>J</i> = 8.7 Hz, 1H), 6.98 (d, <i>J</i> = 8.9 Hz, 1H), 5.59 – 5.41 (m, 1H), 1.45 (d, <i>J</i> = 6.9 Hz, 3H).	353.15
Example 385 Method 6 single unknown stereoisomer	 Rel-(R)-6-((1-(2,3-dichloro-4-fluorophenyl)ethyl)amino)pyrido[3,2-d]pyrimidin-4(3H)-one	white solid, yield: 21.7%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.12 (s, 1H), 7.86 (d, <i>J</i> = 7.6 Hz, 1H), 7.80 (s, 1H), 7.69 (d, <i>J</i> = 8.9 Hz, 1H), 7.51 (dd, <i>J</i> = 8.8, 5.9 Hz, 1H), 7.41 (t, <i>J</i> = 8.7 Hz, 1H), 6.98 (d, <i>J</i> = 8.9 Hz, 1H), 5.61 – 5.40 (m, 1H), 1.45 (d, <i>J</i> = 6.9 Hz, 3H).	353.15 Note: SFC CHIRALPA K AS-H 250mm × 20 mm, 5μm Modifier : IPA: 0.2%NH ₄ O H = 40: 60 Rt=1.8 min
Example 386 Method 6 single unknown stereoisomer	 Rel-(S)-6-((1-(2,3-dichloro-4-fluorophenyl)ethyl)amino)pyrido[3,2-d]pyrimidin-4(3H)-one	white solid, yield: 24.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.12 (s, 1H), 7.86 (d, <i>J</i> = 7.6 Hz, 1H), 7.80 (s, 1H), 7.69 (d, <i>J</i> = 8.9 Hz, 1H), 7.51 (dd, <i>J</i> = 8.9, 5.9 Hz, 1H), 7.41 (t, <i>J</i> = 8.7 Hz, 1H), 6.98 (d, <i>J</i> = 9.0 Hz, 1H), 5.62 – 5.38 (m, 1H), 1.45 (d, <i>J</i> = 6.9 Hz, 3H).	353.15 Note: SFC CHIRALPA K AS-H 250mm × 20 mm, 5μm Modifier : IPA: 0.2%NH ₄ O H = 40: 60 Rt=2.6 min
Example 387 Method 6	 Rel-(S)-6-((1-(2,3-dichloro-4-fluorophenyl)ethyl)amino)pyrido[3,2-d]pyrimidin-4(3H)-one	White solid, yield:	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.04 (s, 1H), 7.81 – 7.75 (m, 1H), 7.69 (d, <i>J</i> = 7.6	355.3 Note: CHIRAL

single unknown stereoisomer	dichloro-6-fluorophenyl)ethyl)amino)pyrido[3,2-d]pyrimidin-4(3H)-one	21.4%	¹ H, 1H), 7.65 (d, <i>J</i> = 8.8 Hz, 1H), 7.54 (dd, <i>J</i> = 8.8, 5.2 Hz, 1H), 7.22 (dd, <i>J</i> = 10.4, 8.8 Hz, 1H), 7.04 (d, <i>J</i> = 9.2 Hz, 1H), 5.77 (q, <i>J</i> = 7.2 Hz, 1H), 1.57 (d, <i>J</i> = 7.2 Hz, 3H).	Cellulose SB 2cm × 25cm, 5μm Modifier : MtBE(0.1% DEA+0.1% FA):(MeOH :DCM=1:1) =85:15 Rt=4.454 min
Example 388 Method 6 single unknown stereoisomer	 Rel-(R)-6-((1-(2,3-dichloro-6-fluorophenyl)ethyl)amino)pyrido[3,2-d]pyrimidin-4(3H)-one	White solid, yield: 27.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.04 (s, 1H), 7.79 (d, <i>J</i> = 3.2 Hz, 1H), 7.69 (d, <i>J</i> = 7.6 Hz, 1H), 7.65 (d, <i>J</i> = 8.8 Hz, 1H), 7.54 (dd, <i>J</i> = 8.8, 5.2 Hz, 1H), 7.22 (dd, <i>J</i> = 10.4, 8.8 Hz, 1H), 7.04 (d, <i>J</i> = 8.8 Hz, 1H), 5.77 (q, <i>J</i> = 7.2 Hz, 1H), 1.57 (d, <i>J</i> = 7.2 Hz, 3H).	355.3 Note: CHIRAL Cellulose SB 2cm × 25cm, 5μm Modifier : MtBE(0.1% DEA+0.1% FA):(MeOH :DCM=1:1) =85:15 Rt=3.778 min

Preparation of

2,3-dichloro-N-(4-methyl-1-oxo-1,2-dihydroisoquinolin-7-yl)benzenesulfonamide (188)

Method 7



Step 1: A mixture of **188-1**, **188-2** (470.36 mg, 3.747 mmol), K_2CO_3 (517.87 mg, 3.747 mmol), and $Pd(dppf)Cl_2$ (91.39 mg, 0.1249 mmol) in 1,4-Dioxane/ H_2O (10:2 mL) was stirred for 16 hour at 100 °C under N_2 . After cooling, the reaction mixture was diluted with water (60 mL), extracted three times with ethyl acetate (20 mL). Organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product that was purified through column chromatography on silica gel (PE/EA=3:1) to give **188-3** (245 mg, 58.48% yield) as a yellow solid. MS (ESI) m/z 335.0 $[M+H]^+$.

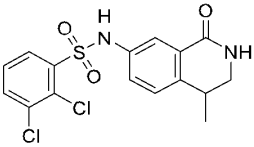
Step 2: A mixture solution of **188-3** (125 mg, 0.3726 mmol), Fe (104.05 mg, 1.863 mmol), NH_4Cl (99.65 mg, 1.863 mmol) and EtOH/ H_2O (10:10 mL) was stirred at 80 °C for 2 hrs. After cooling, the reaction mixture was diluted with water (60 mL), extracted three times with ethyl acetate (20 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product that was purified through column chromatography on silica gel (PE/EA=4:1) to give **188-4** (102 mg, 89.61% yield) as oil. MS (ESI) m/z 305.0 $[M+H]^+$.

Step 3: A mixture solution of **188-4** (92 mg, 0.3012 mmol), 2,3-dichlorobenzenesulfonyl chloride (73.95 mg, 0.3012 mmol), pyridine (71.47 mg, 0.9036 mmol) and DCM (10 mL) was stirred at 25 °C for 16 hrs. After the reaction was completed, the reaction mixture was diluted with water (60 mL) and extracted three times with ethyl acetate (20 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product that was purified through column chromatography on silica gel (PE/EA=5:1) to give **188-5** (129 mg, 83.23% yield) as oil. MS (ESI) m/z 512.9 $[M+H]^+$.

Step 4: A solution of **188-5** (119 mg, 0.2313 mmol) in TFA (10 mL) was stirred for 2 hour at

80 °C. After reaction was completed, the reaction mixture was diluted with water (60 mL), extracted three times with DCM (20 mL). The organic layers were combined, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product that was purified by prep-HPLC (column-Gemini-C18 150 x 21.2 mm, 5µm; Mobile phase: ACN-H₂O (0.1%FA), 40%-60%) to afford the desired product **188** (31.2 mg) as a white solid. MS (ESI) m/z 382.8 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.16 – 11.03 (m, 2H), 8.05 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.97 – 7.88 (m, 2H), 7.59 – 7.50 (m, 3H), 6.90 (d, *J* = 4.8 Hz, 1H), 2.13 (d, *J* = 0.7 Hz, 3H).

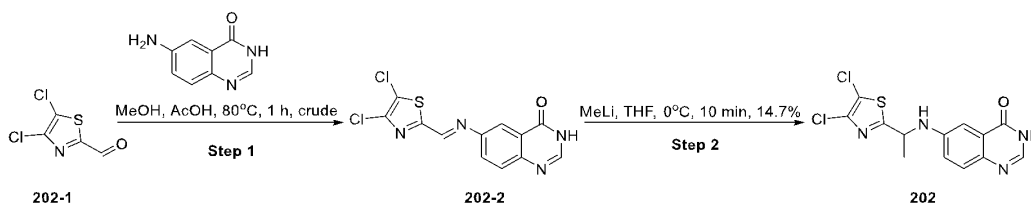
Compound 189 was synthesized using a method similar to that used for Compound **188**.

Example (Compound) No. Method	Structure and Name	Appearance and Yield	¹ H NMR Data	MS (<i>m/z</i>) [M+H] ⁺
Example 189 Method 7 Mixture of Stereoisomers	 2,3-dichloro-N-(4-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	white solid, yield: 4.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.90 (s, 1H), 8.02 (dd, <i>J</i> = 8.0, 1.4 Hz, 1H), 7.93 (dd, <i>J</i> = 8.1, 1.4 Hz, 2H), 7.61 – 7.54 (m, 2H), 7.23 (d, <i>J</i> = 2.0 Hz, 2H), 3.38 (dd, <i>J</i> = 4.8, 3.0 Hz, 1H), 3.04 – 2.92 (m, 2H), 1.15 (d, <i>J</i> = 6.8 Hz, 3H).	385.2

10

Preparation of

6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)quinazolin-4(3H)-one (202) Method 8

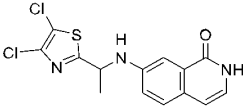


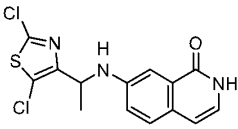
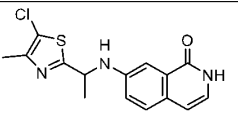
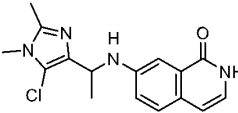
Step 1: To a solution of 6-aminoquinazolin-4(3H)-one (88 mg, 0.54 mmol) in MeOH (5 mL) was added **202-1** (100 mg, 0.55 mmol) and AcOH (0.5 ml). The mixture was stirred at 80 °C

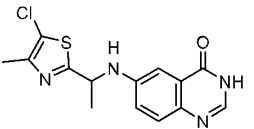
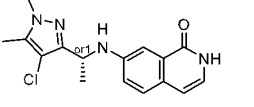
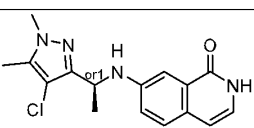
for 1 hour. Water was added and the resulting mixture was extracted with EtOAc, dried over Na_2SO_4 , and concentrated in vacuo to give (E)-6-(((4,5-dichlorothiazol-2-yl)methylene)amino)quinazolin-4(3H)-one **202-2** (100 mg, crude) as a yellow solid without purification. Mass (m/z): 325.40 $[\text{M}+\text{H}]^+$.

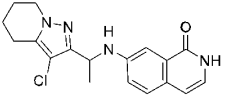
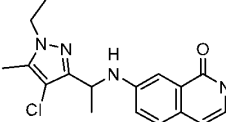
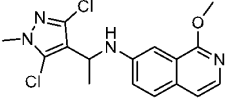
- 5 **Step 2:** To a solution of 203-2 (100 mg, 0.30 mmol) in THF (10ml), was added Methyllithium (0.4 mL, 1.6 M) dropwise at 0 °C. The mixture was stirred at 0 °C for 10 minutes. Water was added and the resulting mixture was extracted with EtOAc, dried over Na_2SO_4 , and concentrated in vacuo. The crude product was purified by prep-HPLC (H_2O : ACN=30:70~100:0; products collected at 60% ACN) to afford **202** (13.5 mg, 14.7% yield) as a
- 10 white solid. Mass (m/z): 341.40 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.97 (brs, 1H), 7.83 (s, 1H), 7.48 (d, $J = 8.8$ Hz, 1H), 7.22 (dd, $J = 8.8, 2.8$ Hz, 1H), 7.10 – 7.04 (m, 2H), 4.86 (p, $J = 6.4$ Hz, 1H), 1.57 (d, $J = 6.8$ Hz, 3H).

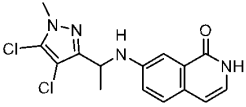
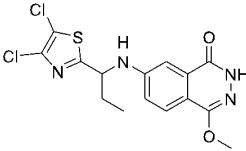
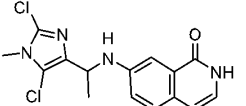
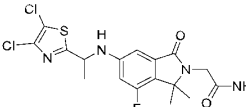
Compounds 187, 190, 207, 214, 216, 226A-226B, 232, 247-248, 256, 272, 308, 328, 338 and 344-346 were synthesized using a method similar to that used for Compound **202**.

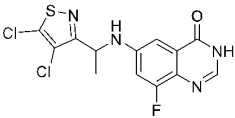
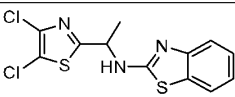
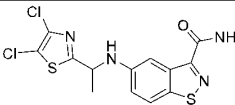
Example (Compound) No. Method	Structure and Name	Appearance and Yield	^1H NMR Data	MS (m/z) $[\text{M}+\text{H}]^+$
Example 187 Method 8 Mixture of Stereoisomers	 7-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)isoquinolin-1(2H)-one	white solid, yield: 7.6%	^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.95 (d, $J = 5.6$ Hz, 1H), 7.44 (d, $J = 8.6$ Hz, 1H), 7.21 (d, $J = 2.6$ Hz, 1H), 7.13 (dd, $J = 8.6, 2.6$ Hz, 1H), 6.92 – 6.86 (m, 2H), 6.39 (d, $J = 7.0$ Hz, 1H), 4.84 (p, $J = 6.6$ Hz, 1H), 1.57 (d, $J = 6.8$ Hz, 3H).	340.1

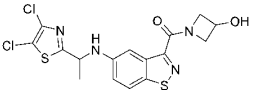
Example 190 Method 8 Mixture of Stereoisomers	 7-((1-(2,5-dichlorothiazol-4-yl)ethyl)amino)isoquinolin-1(2H)-one	white solid, yield: 6.4%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.85 (d, <i>J</i> = 5.5 Hz, 1H), 7.36 (d, <i>J</i> = 8.6 Hz, 1H), 7.23 (d, <i>J</i> = 2.6 Hz, 1H), 7.07 (dd, <i>J</i> = 8.6, 2.6 Hz, 1H), 6.83 (dd, <i>J</i> = 7.0, 5.6 Hz, 1H), 6.57 (d, <i>J</i> = 8.2 Hz, 1H), 6.33 (d, <i>J</i> = 6.9 Hz, 1H), 4.77 (p, <i>J</i> = 7.0 Hz, 1H), 1.49 (d, <i>J</i> = 6.7 Hz, 3H).	340.2
Example 207 Method 8 Mixture of Stereoisomers	 7-((1-(5-chloro-4-methylthiazol-2-yl)ethyl)amino)isoquinolin-1(2H)-one	white solid, yield: 15.3%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.95 (d, <i>J</i> = 5.4 Hz, 1H), 7.42 (d, <i>J</i> = 8.6 Hz, 1H), 7.18 (d, <i>J</i> = 2.5 Hz, 1H), 7.11 (dd, <i>J</i> = 8.6, 2.6 Hz, 1H), 6.90 – 6.81 (m, 2H), 6.37 (d, <i>J</i> = 7.0 Hz, 1H), 4.76 (p, <i>J</i> = 6.7 Hz, 1H), 2.30 (s, 3H), 1.55 (d, <i>J</i> = 6.8 Hz, 3H).	320.2
Example 214 Method 8 Mixture of Stereoisomers	 7-((1-(5-chloro-1,2-dimethyl-1H-imidazol-4-yl)ethyl)amino)isoquinolin-1(2H)-one	white solid, yield: 10.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.83 (d, <i>J</i> = 5.5 Hz, 1H), 7.31 (d, <i>J</i> = 8.6 Hz, 1H), 7.23 (d, <i>J</i> = 2.5 Hz, 1H), 7.06 (dd, <i>J</i> = 8.6, 2.6 Hz, 1H), 6.80 (dd, <i>J</i> = 7.0, 5.3 Hz, 1H), 6.32 (d, <i>J</i> = 7.0 Hz, 1H), 6.28-6.19 (m, 1H), 4.57-4.45 (m, 1H), 3.40 (s, 3H), 2.26 (s, 3H), 1.42 (d, <i>J</i> = 6.7 Hz, 3H).	317.3

Example 216 Method 8 Mixture of Stereoisomers	 6-((1-(5-chloro-4-methylthiazol-2-yl)ethyl)amino)quinazolin-4(3H)-one	white solid, yield: 21.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.93 (s, 1H), 7.81 (s, 1H), 7.46 (d, <i>J</i> = 8.8 Hz, 1H), 7.20 (dd, <i>J</i> = 8.8, 2.8 Hz, 1H), 7.05 (d, <i>J</i> = 2.8 Hz, 1H), 6.98 (d, <i>J</i> = 6.0 Hz, 1H), 4.77 (p, <i>J</i> = 6.6 Hz, 1H), 2.30 (s, 3H), 1.55 (d, <i>J</i> = 6.7 Hz, 3H).	321.2
Example 226A Method 8 single unknown stereoisomer	 rel-(S)-7-((1-(4-chloro-1,5-dimethyl-1H-pyrazol-3-yl)ethyl)amino)isoquinolin-1(2H)-one	Light yellow solid	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.84 (d, <i>J</i> = 5.6 Hz, 1H), 7.32 (d, <i>J</i> = 8.6 Hz, 1H), 7.22 (d, <i>J</i> = 2.5 Hz, 1H), 7.07 (dd, <i>J</i> = 8.6, 2.6 Hz, 1H), 6.80 (dd, <i>J</i> = 7.1, 5.6 Hz, 1H), 6.39 – 6.21 (m, 2H), 4.62 (t, <i>J</i> = 7.1 Hz, 1H), 3.68 (s, 3H), 2.16 (s, 3H), 1.47 (d, <i>J</i> = 6.7 Hz, 3H).	317.2
Example 226B Method 8 single unknown stereoisomer	 rel-(R)-7-((1-(4-chloro-1,5-dimethyl-1H-pyrazol-3-yl)ethyl)amino)isoquinolin-1(2H)-one	white solid, yield: 31.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.84 (d, <i>J</i> = 5.7 Hz, 1H), 7.32 (d, <i>J</i> = 8.6 Hz, 1H), 7.22 (d, <i>J</i> = 2.5 Hz, 1H), 7.07 (dd, <i>J</i> = 8.6, 2.6 Hz, 1H), 6.80 (dd, <i>J</i> = 7.1, 5.7 Hz, 1H), 6.35 – 6.28 (m, 2H), 4.61 (q, <i>J</i> = 6.8 Hz, 1H), 3.68 (s, 3H), 2.16 (s, 3H), 1.47 (d, <i>J</i> = 6.8 Hz, 3H).	317.2

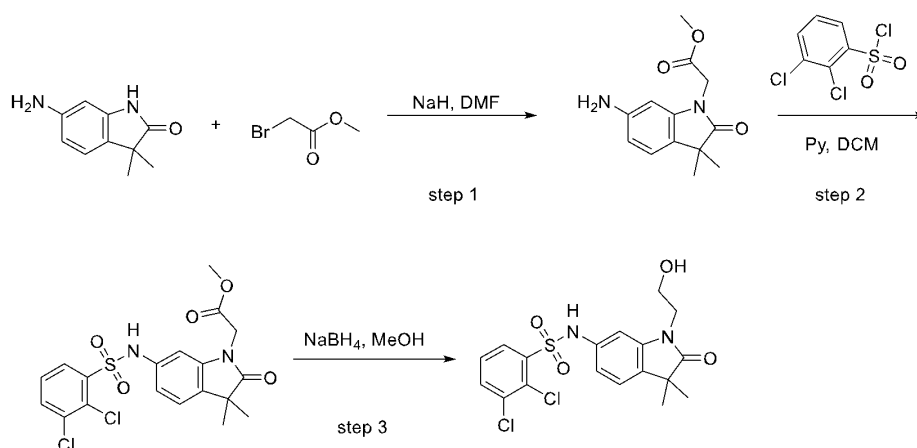
Example 232 Method 8 Mixture of Stereoisomers	 7-((1-(3-chloro-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-2-yl)ethyl)amino)isoquinolin-1(2H)-one	white solid, yield: 11.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.86 (d, <i>J</i> = 5.6 Hz, 1H), 7.33 (d, <i>J</i> = 8.6 Hz, 1H), 7.23 (d, <i>J</i> = 2.5 Hz, 1H), 7.08 (dd, <i>J</i> = 8.6, 2.6 Hz, 1H), 6.81 (dd, <i>J</i> = 7.0, 5.6 Hz, 1H), 6.33 (d, <i>J</i> = 7.4 Hz, 2H), 4.65 (p, <i>J</i> = 6.9 Hz, 1H), 3.97 (td, <i>J</i> = 6.0, 2.3 Hz, 2H), 2.60 (t, <i>J</i> = 6.4 Hz, 2H), 1.96 – 1.87 (m, 2H), 1.83 – 1.70 (m, 2H), 1.48 (d, <i>J</i> = 6.7 Hz, 3H).	343.1
Example 247 Method 8 Mixture of Stereoisomers	 7-((1-(4-chloro-1-ethyl-5-methyl-1H-pyrazol-3-yl)ethyl)amino)isoquinolin-1(2H)-one	white solid, yield: 20.3%	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 9.13 (s, 1H), 7.58 (d, <i>J</i> = 2.5 Hz, 1H), 7.36 (d, <i>J</i> = 8.6 Hz, 1H), 7.08 (dd, <i>J</i> = 8.6, 2.5 Hz, 1H), 6.86 – 6.80 (m, 1H), 6.43 (d, <i>J</i> = 7.1 Hz, 1H), 4.87 (q, <i>J</i> = 6.7 Hz, 1H), 4.03 (q, <i>J</i> = 7.2 Hz, 2H), 2.20 (s, 3H), 1.59 (d, <i>J</i> = 6.7 Hz, 3H), 1.36 (t, <i>J</i> = 7.3 Hz, 3H).	331.3
Example 248 Method 8 Mixture of Stereoisomers	 N-(1-(3,5-dichloro-1-methyl-1H-pyrazol-4-yl)ethyl)-1-methoxyisoquinolin-7-amine	white solid, yield: 18.3%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.64 (d, <i>J</i> = 5.7 Hz, 1H), 7.56 (d, <i>J</i> = 8.9 Hz, 1H), 7.19 (dd, <i>J</i> = 8.8, 2.4 Hz, 1H), 7.10 (d, <i>J</i> = 5.7 Hz, 1H), 6.89 (d, <i>J</i> = 2.4 Hz, 1H), 6.67 (d, <i>J</i> = 6.7 Hz, 1H), 4.51 (p, <i>J</i> = 6.9 Hz, 1H), 3.96 (s, 3H), 3.70 (s, 3H), 1.54 (d, <i>J</i> = 6.9 Hz, 3H).	351.1

Example 256 Method 8 Mixture of Stereoisomers	 7-((1-(4,5-dichloro-1-methyl-1H-pyrazol-3-yl)ethyl)amino)isoquinolin-1(2H)-one	white solid, yield: 15.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.86 (d, <i>J</i> = 5.5 Hz, 1H), 7.34 (d, <i>J</i> = 8.6 Hz, 1H), 7.23-7.18 (m, 1H), 7.07 (dd, <i>J</i> = 8.6, 2.6 Hz, 1H), 6.81 (t, <i>J</i> = 6.3 Hz, 1H), 6.44 (d, <i>J</i> = 7.6 Hz, 1H), 6.33 (d, <i>J</i> = 7.0 Hz, 1H), 4.66 (p, <i>J</i> = 6.9 Hz, 1H), 3.77 (s, 2H), 1.50 (d, <i>J</i> = 6.8 Hz, 3H).	337.2
Example 272 Method 8 Mixture of Stereoisomers	 7-((1-(4,5-dichlorothiazol-2-yl)propyl)amino)-4-methoxyphthalazin-1(2H)-one	white solid, yield: 13.4%	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.81 (d, <i>J</i> = 8.7 Hz, 1H), 7.30 (d, <i>J</i> = 2.5 Hz, 1H), 7.26 (dd, <i>J</i> = 8.8, 2.5 Hz, 1H), 4.70 (dd, <i>J</i> = 8.4, 5.2 Hz, 1H), 3.93 (s, 3H), 2.15 – 1.95 (m, 2H), 1.10 (t, <i>J</i> = 7.4 Hz, 3H).	385.03
Example 308 Method 8 Mixture of Stereoisomers	 7-((1-(2,5-dichloro-1-methyl-1H-imidazol-4-yl)ethyl)amino)isoquinolin-1(2H)-one	brown solid, yield: 10.7%	¹ H NMR (400 MHz, CDCl ₃) δ 9.62 (s, 1H), 7.56 (s, 1H), 7.34 (d, <i>J</i> = 8.6 Hz, 1H), 7.02 (dd, <i>J</i> = 8.5, 2.3 Hz, 1H), 6.86 (s, 1H), 6.41 (d, <i>J</i> = 7.1 Hz, 1H), 4.80 (d, <i>J</i> = 6.8 Hz, 1H), 4.59 (s, 1H), 3.51 (s, 3H), 1.53 (d, <i>J</i> = 6.5 Hz, 3H).	352.8
Example 328 Method 8 Mixture of Stereoisomers	 2-(5-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-7-fluoro-1,1-dimethyl-3-oxoisindolin-2-yl)acetamide	white solid, yield: 6.7%	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 6.77 (d, <i>J</i> = 1.9 Hz, 1H), 6.62 (dd, <i>J</i> = 11.9, 2.0 Hz, 1H), 4.75 (q, <i>J</i> = 6.8 Hz, 1H), 4.11 (d, <i>J</i> = 2.5 Hz, 2H), 1.62 (d, <i>J</i> = 6.8 Hz, 3H), 1.51 (s, 6H)	432.1

Example 338 Method 8 Mixture of Stereoisomers	 6-((1-(4,5-dichloro-2-isothiazol-3-yl)ethyl)amino)-8-fluoroquinazolin-4(3H)-one	white solid, yield: 18%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.05 (s, 1H), 7.80 (d, <i>J</i> = 3.3 Hz, 1H), 7.06 – 6.96 (m, 2H), 6.88 (d, <i>J</i> = 2.6 Hz, 1H), 4.89 (t, <i>J</i> = 6.9 Hz, 1H), 1.54 (d, <i>J</i> = 6.8 Hz, 3H).	359.1
Example 344 Method 8 Mixture of Stereoisomers	 N-(1-(4,5-dichloro-2-thiazol-2-yl)ethyl)benzo[d]thiazol-2-amine	yellow solid, yield: 8.8%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.88 (d, <i>J</i> = 6.6 Hz, 1H), 7.74 (d, <i>J</i> = 7.8 Hz, 1H), 7.43 (d, <i>J</i> = 8.0 Hz, 1H), 7.29 – 7.21 (m, 1H), 7.08 (t, <i>J</i> = 7.6 Hz, 1H), 5.32 (t, <i>J</i> = 6.8 Hz, 1H), 1.59 (d, <i>J</i> = 7.0 Hz, 3H).	330.0
Example 345 Method 8 Mixture of Stereoisomers	 5-[1-(4,5-dichloro-2-thiazol-2-yl)ethylamino]-1,2-benzothiazole-3-carboxamide	yellow solid, yield: 12.4%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.06 – 8.01 (m, 1H), 7.98 (d, <i>J</i> = 8.9 Hz, 1H), 7.85 (d, <i>J</i> = 2.2 Hz, 1H), 7.60 (s, 1H), 7.13 (dd, <i>J</i> = 8.9, 2.3 Hz, 1H), 7.00 (d, <i>J</i> = 5.8 Hz, 1H), 4.81 (p, <i>J</i> = 6.6 Hz, 1H), 1.58 (d, <i>J</i> = 6.6 Hz, 3H).	372.9

Example 346		yellow solid, yield: 14.5%	^1H NMR (400 MHz, DMSO) δ 7.99 (d, J = 8.8 Hz, 1H), 7.74 (s, 1H), 7.14 (d, J = 9.0 Hz, 1H), 7.00 (s, 1H), 5.75 (d, J = 6.4 Hz, 1H), 4.80 (t, J = 6.1 Hz, 1H), 4.67 (d, J = 9.0 Hz, 1H), 4.51 (s, 1H), 4.31 – 4.18 (m, 2H), 3.85 – 3.77 (m, 1H), 1.57 (d, J = 6.7 Hz, 3H).	428.9
Method 8				
Mixture of Stereoisomers	(5-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)benzo[d]isothiazol-3-yl)(3-hydroxyazetidin-1-yl)methanone			

Preparation of 2,3-dichloro-N-(1-(2-hydroxyethyl)-3,3-dimethyl-2-oxoindolin-6-yl)benzenesulfonamide (240) Method 9



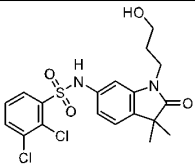
- Step 1:** To a solution of methyl 2-bromoacetate (1.00 eq, 153 mg, 0.999 mmol) in DMF (2 mL) was added sodium hydride (60%; 1.00 eq, 40 mg, 0.999 mmol) at 0 °C and then methyl 2-bromoacetate (1.00 eq, 153 mg, 0.999 mmol) was added. The reaction was stirred for 2 h at the same temperature. The reaction was then quenched with 0.5N HCl and extracted with ethyl acetate twice. The combined organic layers were washed with brine twice, dried over sodium sulfate and concentrated under vacuum to afford methyl 2-(6-amino-3,3-dimethyl-2-oxoindolin-1-yl)acetate (240 mg, 0.97 mmol, 96.8% yield) as a yellow oil. Mass (m/z): 249.2 $[\text{M}+\text{H}]^+$.

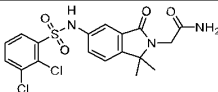
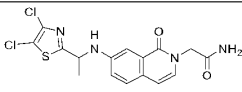
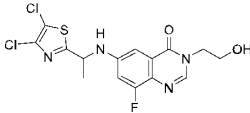
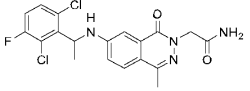
Step 2: Methyl 2-[6-[(2,3-dichlorophenyl)sulfonylamino]-3,3-dimethyl-2-oxoindolin-1-

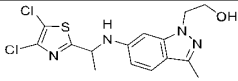
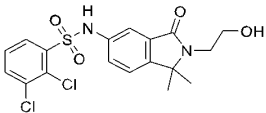
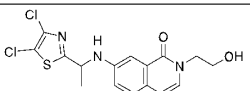
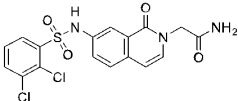
yl]acetate (400 mg, 0.875 mmol, 87.56 % yield) was obtained as a brown solid using Method 1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.80 (s, 1H), 8.05 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.94 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 6.73 (dd, *J* = 7.9, 1.9 Hz, 1H), 6.64 (d, *J* = 1.9 Hz, 1H), 4.47 (s, 2H), 3.67 (s, 3H), 1.21 (s, 6H).

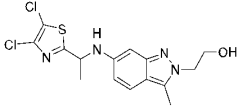
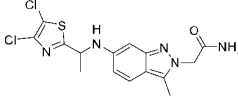
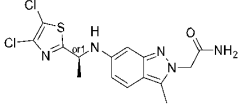
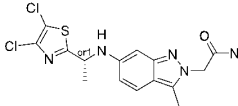
- 5 **Step 3:** To a solution of methyl 2-[6-[(2,3-dichlorophenyl)sulfonylamino]-3,3-dimethyl-2-oxo-indolin-1-yl]acetate (1.00 eq, 70 mg, 0.15 mmol) in methanol (5 mL) was added NaBH₄ (3.00 eq, 17 mg, 0.459 mmol) and stirred overnight at 60 °C. The reaction was quenched with water, extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under vacuum. The residue was purified by Prep-HPLC
- 10 to afford 2,3-dichloro-N-[1-(2-hydroxyethyl)-3,3-dimethyl-2-oxo-indolin-6-yl]benzenesulfonamide (11 mg, 0.025 mmol, 16.1% yield) as a white solid. Mass (m/z): 429.3 [M+H]⁺, ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.99 (s, 1H), 8.07 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.90 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 2.0 Hz, 1H), 6.67 (dd, *J* = 8.0, 1.9 Hz, 1H), 4.84 (s, 1H), 3.60 (t, *J* = 6.0 Hz, 2H), 3.49 (t, *J* = 4.9 Hz,
- 15 2H), 1.17 (s, 6H).

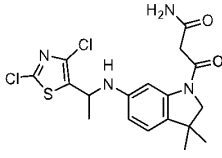
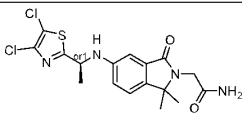
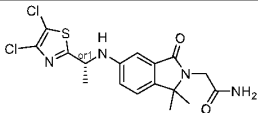
Compounds **273**, **289-290**, **297**, **300-301**, **303**, **305-307**, **312**, **312A**, **312B**, **317**, **320**, **320A**, **323**, **323A**, **327**, **329**, **331-332**, **334-337**, **339-341**, **341A**, **341B**, **343**, **347-348**, **347A**, **355**, **355A**, **355B**, **357-358**, **361-368**, **376-381** and **389-391** were synthesized using a method similar to that used for Compound **240**.

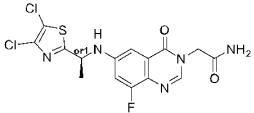
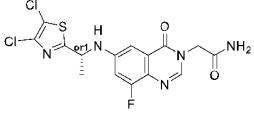
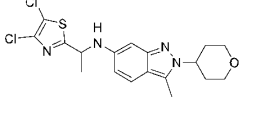
Example (Compound) No. Method	Structure and Name	Appearance and Yield	¹ H NMR Data	MS (m/z) [M+H] ⁺
Example 273 Method 9		white solid, yield: 16.1%	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.01 (dd, <i>J</i> = 8.0, 1.5 Hz, 1H), 7.70 (dd, <i>J</i> = 8.1, 1.5 Hz, 1H), 7.36 (t, <i>J</i> = 8.0 Hz, 1H), 7.06 (d, <i>J</i> = 8.0 Hz, 1H), 6.80 (d, <i>J</i> = 1.8 Hz, 1H), 6.75 (dd, <i>J</i> = 8.0, 1.9 Hz, 1H), 3.68 (t, <i>J</i> = 7.0 Hz, 2H), 3.49 (t, <i>J</i> = 6.3 Hz, 2H), 1.77 – 1.66	443.1

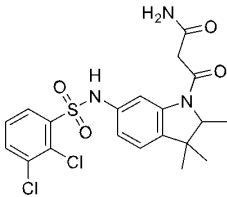
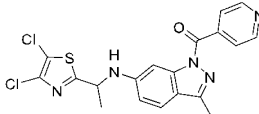
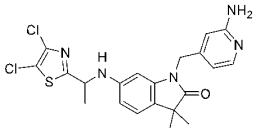
			(m, 2H), 1.19 (s, 6H).	
Example 289 Method 9	 2-(5-((2,3-dichlorophenyl)sulfonylamido)-1,1-dimethyl-3-oxoisindolin-2-yl)acetamide	white solid, yield: 55.9%	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.98 (dd, <i>J</i> = 7.9, 1.2 Hz, 1H), 7.65 (dd, <i>J</i> = 8.1, 1.2 Hz, 1H), 7.44 (d, <i>J</i> = 1.7 Hz, 1H), 7.39 – 7.27 (m, 3H), 4.02 (s, 2H), 1.32 (s, 6H).	442.0
Example 290 Method 9 Mixture of Stereoisomers	 2-(7-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-1-oxoisquinolin-2(1H)-yl)acetamide	Yellow solid, yield: 55.6%	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.48 (d, <i>J</i> = 8.8 Hz, 1H), 7.33 (d, <i>J</i> = 2.4 Hz, 1H), 7.18 (dd, <i>J</i> = 2.4 Hz, <i>J</i> = 8.4 Hz, 1H), 7.07 (d, <i>J</i> = 7.6 Hz, 1H), 6.59 (d, <i>J</i> = 7.2 Hz, 1H), 4.82 - 4.79 (m, 1H), 4.71 - 4.62 (m, 2H), 1.66 (d, <i>J</i> = 6.8 Hz, 3H).	396.8
Example 297 Method 9 Mixture of Stereoisomers	 6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-8-fluoro-3-(2-hydroxyethyl)quinazolin-4(3H)-one	White solid, yield: 7.4%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.03 (s, 1H), 7.26 (d, <i>J</i> = 6.4 Hz, 1H), 7.10 (dd, <i>J</i> = 12.6, 2.5 Hz, 1H), 6.99 (d, <i>J</i> = 2.6 Hz, 1H), 4.95 (p, <i>J</i> = 6.6 Hz, 1H), 3.98 (t, <i>J</i> = 5.3 Hz, 2H), 3.63 (t, <i>J</i> = 5.3 Hz, 2H), 1.57 (d, <i>J</i> = 6.7 Hz, 3H).	403.8
Example 300 Method 9 Mixture of Stereoisomers	 2-(7-((1-(2,6-dichloro-3-fluorophenyl)ethyl)amino)-4-methyl-1-oxophthalazin-2(1H)-yl)acetamide	Light yellow solid, yield: 4.3%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.63 (d, <i>J</i> = 8.8 Hz, 1H), 7.49 (d, <i>J</i> = 7.2 Hz, 1H), 7.44 (s, 1H), 7.36 (t, <i>J</i> = 8.8 Hz, 1H), 7.14 – 7.01 (m, 3H), 5.32 (t, <i>J</i> = 7.2 Hz, 1H), 4.52 (s, 2H), 2.35	423.1/425.1

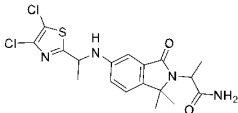
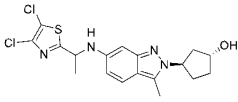
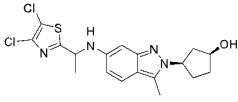
			(s, 3H), 1.64 (d, $J = 7.2$ Hz, 3H).	
Example 301 Method 9 Mixture of Stereoisomers	 2-(6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-3-methyl-1H-indazol-1-yl)ethan-1-ol	white solid, yield: 9.74%	^1H NMR (400 MHz, CDCl_3) δ 7.52 (d, $J = 8.8$ Hz, 1H), 6.66 – 6.61 (m, 1H), 6.31 (d, $J = 1.6$ Hz, 1H), 4.97 – 4.76 (m, 1H), 4.53 – 4.36 (m, 2H), 4.12 – 3.83 (m, 2H), 2.60 (s, 3H), 1.74 (d, $J = 6.8$ Hz, 3H).	372.8
Example 303 Method 9	 2-(6-((1-(4,5-dichlorophenyl)sulfonyl)ethyl)amino)-3-methyl-1H-indazol-1-yl)ethan-1-ol	white solid, yield: 14.9%	^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.04 (s, 1H), 8.06 (dd, $J = 8.0$, 1.5 Hz, 1H), 7.94 (dd, $J = 8.1$, 1.5 Hz, 1H), 7.60 – 7.52 (m, 2H), 7.35 – 7.29 (m, 2H), 4.69 (d, $J = 50.3$ Hz, 1H), 3.54 (d, $J = 6.7$ Hz, 2H), 3.39 (d, $J = 6.7$ Hz, 2H), 1.36 (s, 6H).	429.0
Example 305 Method 9 Mixture of Stereoisomers	 7-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-2-(2-hydroxyethyl)isoquinolin-1(2H)-one	white solid, yield: 52.6%	^1H NMR (400 MHz, CDCl_3) δ 7.71 (s, 1H), 7.42 (d, $J = 8.4$ Hz, 1H), 7.13 – 7.07 (m, 1H), 6.97 (d, $J = 7.2$ Hz, 1H), 6.48 (d, $J = 7.2$ Hz, 1H), 4.88 (q, $J = 6.8$ Hz, $J = 13.6$ Hz, 1H), 4.20 – 4.18 (m, 2H), 3.99 (t, $J = 5.2$ Hz, 2H), 1.74 (d, $J = 6.8$ Hz, 3H).	383.8
Example 306 Method 9	 2-(7-((2,3-dichlorophenyl)sulfonyl)amido)-1H-indazol-1-yl)ethan-1-ol	White solid, yield: 67.3%	^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.10 (s, 1H), 8.04 (d, $J = 7.2$ Hz, 1H), 7.90 (d, $J = 6.8$ Hz, 2H), 7.56–7.52 (m, 3H),	425.8

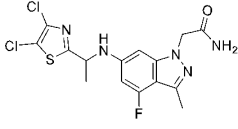
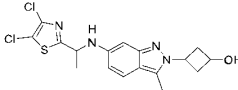
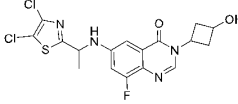
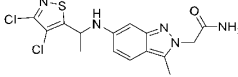
	oxoisoquinolin-2(1H)-yl)acetamide		7.49-7.48 (m, 1H), 7.27 (d, $J = 7.2$ Hz, 1H), 7.18 (s, 1H), 6.49 (d, $J = 7.2$ Hz, 1H), 4.51 (s, 2H).	
Example 307 Method 9 Mixture of Stereoisomers	 2-(6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-3-methyl-2H-indazol-2-yl)ethan-1-ol	white solid, yield: 11.26 %	^1H NMR (400 MHz, CDCl_3) δ 7.43 (d, $J = 8.8$ Hz, 1H), 6.52-6.56 (m, 1H), 6.53 (s, 1H), 4.79 (d, $J = 6.8$ Hz, 1H), 4.53 – 4.46 (m, 2H), 4.42 (s, 1H), 4.10 (t, $J = 4.8$ Hz, 2H), 2.58 (s, 3H), 1.69 (d, $J = 6.4$ Hz, 3H).	372.8
Example 312A Method 9 Mixture of stereoisomers	 2-(6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-3-methyl-2H-indazol-2-yl)acetamide	White solid, yield: 55.91 %	^1H NMR (400 MHz, CDCl_3) δ 7.46 (d, $J = 9.2$ Hz, 1H), 7.06 (d, 1H), 6.68-6.58 (m, 1H), 6.50 (d, $J = 1.6$ Hz, 1H), 5.48 (s, 1H), 5.07 (s, 2H), 4.86-4.73 (m, 1H), 4.44 (s, 1H), 2.63 (s, 3H), 1.72 (d, $J = 6.8$ Hz, 3H).	383.8, 385.9
Example 312 Method 9 single unknown stereoisomer	 rel-(R)-2-(6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-3-methyl-2H-indazol-2-yl)acetamide	White solid, yield: 23%	^1H NMR (400 MHz, CDCl_3) δ 7.46 (d, $J = 9.2$ Hz, 1H), 7.06 (d, 1H), 6.68-6.58 (m, 1H), 6.50 (d, $J = 1.6$ Hz, 1H), 5.48 (s, 1H), 5.07 (s, 2H), 4.86-4.73 (m, 1H), 4.44 (s, 1H), 2.63 (s, 3H), 1.72 (d, $J = 6.8$ Hz, 3H).	383.8, 385.9 Note: CHIRAL PAK IC, 2cm*25c m, 5um, EtOH, MtBE, 20mL/min, Rt = 5.78 min.
Example 312B Method 9 single unknown	 rel-(S)-2-(6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-3-methyl-2H-indazol-2-yl)acetamide	yellow solid., yield: 23.53 %	^1H NMR (400 MHz, CDCl_3) δ 7.43 (d, $J = 9.2$ Hz, 1H), 6.84 (s, 1H), 6.63-6.58 (m, 1H), 6.46 (d, $J = 2.0$ Hz, 1H), 5.47	383.8, 385.8 CHIRAL PAK IC, 2cm*25c

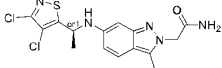
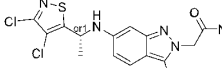
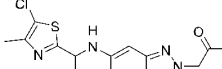
stereoisomer	dichlorothiazol-2-yl)ethyl)amino)-3-methyl-2H-indazol-2-yl)acetamide		(s, 1H), 5.00 (s, 2H), 4.82-4.72 (m, 1H), 4.38 (s, 1H), 2.59 (s, 3H), 1.69 (d, $J = 6.8$ Hz, 3H).	m, 5 μ m, EtOH, MtBE, 20mL/min, Rt = 3.0 min
Example 317 Method 9 Mixture of Stereoisomers	 3-(6-((1-(2,4-dichlorothiazol-5-yl)ethyl)amino)-3,3-dimethylindolin-1-yl)-3-oxopropanamide	White solid, yield: 37%	^1H NMR (400 MHz, DMSO- d_6) δ 7.51 (s, 1H), 7.45 (d, $J = 2.2$ Hz, 1H), 7.07 (s, 1H), 6.93 (d, $J = 8.1$ Hz, 1H), 6.42 (d, $J = 5.1$ Hz, 1H), 6.16 (dd, $J = 8.1, 2.2$ Hz, 1H), 4.66 – 4.52 (m, 1H), 3.80 (s, 2H), 3.33 (s, 2H), 1.49 (d, $J = 6.7$ Hz, 3H), 1.20 (s, 6H).	427.05
Example 320 Method 9 single unknown stereoisomer	 rel-(R)-2-(5-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-1,1-dimethyl-3-oxoisindolin-2-yl)acetamide	White solid, yield: 50.1%	^1H NMR (400 MHz, Methanol- d_4) δ 7.33 (d, $J = 8.3$ Hz, 1H), 6.96 (d, $J = 8.4$ Hz, 1H), 6.91 (s, 1H), 4.78 – 4.69 (m, 1H), 4.12 (s, 2H), 1.63 (d, $J = 6.7$ Hz, 3H), 1.44 (s, 6H).	413.05 CHIRALPA K IF 2cm $\times$ 25cm, 5 μ m, Mobile Phase A: MtBE Phase B: MeOH:DCM Flow Rate: 20mL/min 220nm, 25 $^\circ$ C Rt: 3.836 min.
Example 320A Method 9 single	 rel-(S)-2-(5-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-1,1-dimethyl-3-oxoisindolin-2-yl)acetamide	White solid, yield: 50.1%	^1H NMR (400 MHz, Methanol- d_4) δ 7.33 (d, $J = 8.3$ Hz, 1H), 6.95 (d, $J = 8.4$ Hz, 1H), 6.90 (s, 1H), 4.78 – 4.69 (m, 1H), 4.12 (s, 2H), 1.63 (d, $J = 6.7$ Hz, 3H), 1.44 (s, 6H).	413.05 CHIRALPA K IF 2cm $\times$ 25cm, 5 μ m, Mobile Phase A: MtBE Phase B: MeOH:DCM Flow Rate: 20mL/min 220nm, 25 $^\circ$ C Rt: 3.836 min.

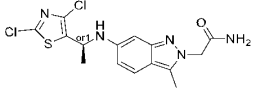
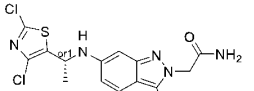
unknown stereoisomer	dichlorothiazol-2-yl)ethyl)amino)-1,1-dimethyl-3-oxoisindolin-2-yl)acetamide		1H), 4.78 – 4.68 (m, 1H), 1.63 (d, $J = 6.7$ Hz, 3H), 1.43 (s, 6H).	Sum, Mobile Phase A: MtBE Phase B: MeOH:DC M Flow Rate:20m L/min 220nm,25 °C Rt:3.249 min.
Example 323 Method 9 single unknown stereoisomer	 rel-(R)-2-(6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-8-fluoro-4-oxoquinazolin-3(4H)-yl)acetamide	White solid, yield: 11.8%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.04 (s, 1H), 7.76 – 7.68 (m, 1H), 7.31 – 7.24 (m, 2H), 7.11 (dd, $J = 12.6$, 2.6 Hz, 1H), 6.96 (d, $J = 2.5$ Hz, 1H), 4.94 (t, $J = 6.6$ Hz, 1H), 4.55 (s, 2H), 1.56 (d, $J = 6.6$ Hz, 3H).	416.9 Note: SFC column, RT = 7.14 min
Example 323A Method 9 single unknown stereoisomer	 rel-(S)-2-(6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-8-fluoro-4-oxoquinazolin-3(4H)-yl)acetamide	White solid, yield: 11.8%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.04 (s, 1H), 7.76 – 7.68 (m, 1H), 7.31 – 7.24 (m, 2H), 7.11 (dd, $J = 12.6$, 2.6 Hz, 1H), 6.96 (d, $J = 2.5$ Hz, 1H), 4.94 (t, $J = 6.6$ Hz, 1H), 4.55 (s, 2H), 1.56 (d, $J = 6.6$ Hz, 3H).	416.9 Note: SFC column, RT = 8.19 min
Example 327 Method 9 Mixture of Stereoisomers	 N-(1-(4,5-dichlorothiazol-2-	White solid, yield: 54%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.40 (d, $J = 9.4$ Hz, 1H), 6.60 (dd, $J = 9.0$, 2.0 Hz, 1H), 6.51 (d, $J = 5.5$ Hz, 1H), 6.19	411.2

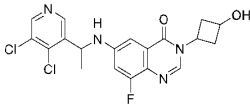
	yl)ethyl)-3-methyl-2-(tetrahydro-2H-pyran-4-yl)-2H-indazol-6-amine		(d, $J = 2.1$ Hz, 1H), 4.78 – 4.70 (m, 1H), 4.62 – 4.49 (m, 1H), 3.96 (d, $J = 11.6$ Hz, 2H), 3.50 (td, $J = 11.9, 2.1$ Hz, 2H), 2.52 (s, 3H), 2.21 – 2.02 (m, 2H), 1.78 (d, $J = 12.9$ Hz, 2H), 1.55 (d, $J = 6.8$ Hz, 3H).	
Example 329 Method 9 Mixture of Stereoisomers	 3-(6-((2,3-dichlorophenyl)sulfonamido)-2,3,3-trimethylindolin-1-yl)-3-oxopropanamide	White solid, yield: 4%	^1H NMR (400 MHz, CDCl_3) δ 8.04 (m, 1H), 7.89 (s, 1H), 7.74 (d, $J = 8.0$ Hz, 1H), 7.38 (m, 1H), 7.04 (d, $J = 8.0$ Hz, 1H), 6.89 (d, $J = 8.0$ Hz, 1H), 4.19 (d, $J = 4.0$ Hz, 1H), 1.27 (s, 3H), 1.13 (m, 6H).	470.1
Example 331 Method 9 Mixture of Stereoisomers	 (6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-3-methyl-1H-indazol-1-yl)(pyridin-4-yl)methanone	White solid, yield: 2.1%	^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.80 – 8.73 (m, 2H), 7.79 (dd, $J = 4.4, 1.6$ Hz, 2H), 7.62 (d, $J = 8.6$ Hz, 1H), 7.57 (s, 1H), 7.36 (d, $J = 6.0$ Hz, 1H), 6.87 (dd, $J = 8.6, 2.0$ Hz, 1H), 4.94 – 4.90 (m, 1H), 1.60 (d, $J = 6.8$ Hz, 3H), 1.23 (s, 3H).	432.0
Example 332 Method 9 Mixture of Stereoisomers	 2,3-dichloro-N-(1,3,3-trimethyl-2-oxoindolin-6-yl)benzenesulfonamid	white solid, yield: 4.9%	^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.80 (d, $J = 5.2$ Hz, 1H), 7.07 (d, $J = 8.0$ Hz, 1H), 6.56 (d, $J = 5.6$ Hz, 1H), 6.31 (d, $J = 5.2$ Hz, 1H), 6.20 (dd, $J = 8.2, 1.8$ Hz, 1H), 6.17 – 6.11 (m, 2H), 5.98 (s, 2H), 4.73 – 4.56 (m,	462.1

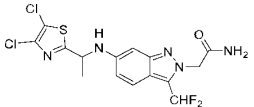
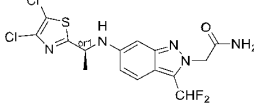
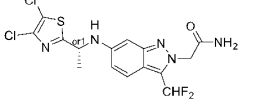
	c		3H), 1.47 (d, $J = 6.8$ Hz, 3H), 1.28 (d, $J = 4.6$ Hz, 6H).	
Example 334 Method 9 Mixture of Stereoisomers	 2-(5-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-1,1-dimethyl-3-oxoisindolin-2-yl)propanamide	White solid, yield: 20.04 %	^1H NMR (400 MHz, DMSO- d_6) δ 7.34 (d, $J = 8.2$ Hz, 1H), 7.01 – 6.93 (m, 2H), 6.93 – 6.86 (m, 1H), 6.78 (dd, $J = 5.6$, 1.3 Hz, 1H), 6.72 (dd, $J = 12.0$, 2.2 Hz, 1H), 4.82 – 4.74 (m, 1H), 4.09 – 4.01 (m, 1H), 1.54 (d, 3H), 1.49 (dd, $J = 7.1$, 2.2 Hz, 3H), 1.42 (d, $J = 2.3$ Hz, 3H), 1.37 (d, $J = 1.9$ Hz, 3H).	427.15
Example 335 Method 9 Mixture of Stereoisomers	 3-(6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-3-methyl-2H-indazol-2-yl)cyclopentan-1-ol	off-white solid, yield: 7.75%	^1H NMR (400 MHz, Methanol- d_4) δ 7.39 (d, $J = 8.8$ Hz, 1H), 6.69 – 6.56 (m, 1H), 6.25 (d, $J = 1.6$ Hz, 1H), 5.05 – 4.95 (m, 1H), 4.74 – 4.63 (m, 1H), 4.36 – 4.24 (m, 1H), 2.54 (s, 3H), 2.45 – 2.32 (m, 1H), 2.30 – 2.20 (m, 1H), 2.18 – 2.02 (m, 2H), 1.99 – 1.81 (m, 2H), 1.63 (d, $J = 6.8$ Hz, 3H)	412.9
Example 336 Method 9 Mixture of Stereoisomers	 3-(6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-3-methyl-2H-indazol-2-yl)cyclopentan-1-ol	off-white solid, yield: 10.6%	^1H NMR (400 MHz, Methanol- d_4) δ 7.39 (d, $J = 8.8$ Hz, 1H), 6.62 (d, $J = 7.6$ Hz, 1H), 6.25 (s, 1H), 5.06 – 4.95 (m, 1H), 4.72 – 4.64 (m, 1H), 4.36 – 4.27 (m, 1H), 2.54 (s, 3H), 2.45 – 2.33 (m, 1H), 2.24 – 2.18	412.9

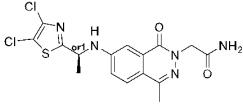
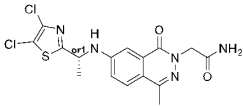
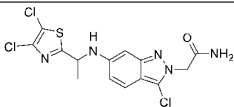
			(m, 1H), 2.16 – 2.04 (m, 2H), 1.98 – 1.86 (m, 2H), 1.63 (d, $J = 6.8$ Hz, 3H).	
Example 337 Method 9 Mixture of Stereoisomers	 2-(6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-4-fluoro-3-methyl-1H-indazol-1-yl)acetamide	yellow solid, yield: 11.4%	^1H NMR (400 MHz, DMSO- d_6) 7.38 (s, 1H), 7.19 (s, 1H), 6.90 (d, $J = 6.4$ Hz, 1H), 6.36-6.34 (m, 2H), 4.91-4.87 (m, 1H), 4.72 (s, 2H), 2.41 (s, 3H), 1.55 (d, $J = 6.4$ Hz, 3H).	401.9
Example 339 Method 9 Mixture of Stereoisomers	 3-(6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-3-methyl-2H-indazol-2-yl)cyclobutan-1-ol	white solid, yield: 16.3%	^1H NMR (400 MHz, CDCl_3) δ 7.38 (d, $J = 8.8$ Hz, 1H), 6.57 (s, 1H), 6.56 – 6.51 (m, 1H), 4.82 – 4.74 (m, 1H), 4.63 – 4.53 (m, 1H), 4.29 – 4.20 (m, 2H), 3.07 – 2.97 (m, 2H), 2.82 – 2.72 (m, 2H), 2.51 (s, 3H), 1.68 (d, $J = 6.8$ Hz, 3H).	397.0
Example 340 Method 9 Mixture of Stereoisomers	 6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-8-fluoro-3-(3-hydroxycyclobutyl)quinazolin-4(3H)-one	white solid, yield: 66.7%	^1H NMR (400 MHz, CD_3OD) δ 8.11 (d, $J = 2.4$ Hz, 1H), 7.03 - 7.00 (m, 2H), 4.83 - 4.81 (m, 1H), 4.47 - 4.46 (m, 1H), 4.14 - 4.12 (m, 1H), 2.93 - 2.92 (m, 2H), 2.24 - 2.23 (m, 2H), 1.64 - 1.63 (m, 3H).	429.1
Example 341 Method 9 Mixture of Stereoisomers	 2-(6-((1-(3,4-dichloroisothiazol-5-yl)ethyl)amino)-4-fluoro-3-methyl-1H-indazol-1-yl)acetamide	White solid, yield: 15%	^1H NMR (400 MHz, Chloroform- d) δ 7.40 (d, $J = 8.9$ Hz, 1H), 6.54 (d, $J = 2.1$ Hz, 1H), 6.46 (s, 1H), 6.32 (d, $J = 2.3$ Hz,	384.02

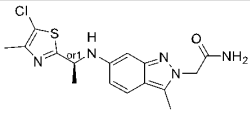
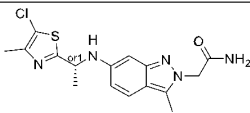
	yl)ethyl)amino)-3-methyl-2H-indazol-2-yl)acetamide		¹ H), 5.46 (s, 1H), 4.92 (d, <i>J</i> = 1.5 Hz, 2H), 4.85 (q, <i>J</i> = 7.4 Hz, 1H), 4.25 (s, 1H), 2.55 (s, 3H), 1.69 (d, <i>J</i> = 6.8 Hz, 3H).	
Example 341A Method 9 single unknown stereoisomer	 rel-(S)-2-(6-((1-(3,4-dichloroisothiazol-5-yl)ethyl)amino)-3-methyl-2H-indazol-2-yl)acetamide	White solid	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.51 (s, 1H), 7.40 (d, <i>J</i> = 8.9 Hz, 1H), 7.27 – 7.18 (m, 1H), 6.63 – 6.55 (m, 2H), 5.99 (d, <i>J</i> = 1.8 Hz, 1H), 4.82 (s, 2H), 4.80 – 4.72 (m, 1H), 2.43 (s, 3H), 1.59 (d, <i>J</i> = 6.7 Hz, 3H).	384.28 CHIRALP AK ID column, 2cm × 25cm, 5μm, MTBE: IPA. 20mL/min, Rt=2.268 min
Example 341B Method 9 single unknown stereoisomer	 rel-(R)-2-(6-((1-(3,4-dichloroisothiazol-5-yl)ethyl)amino)-3-methyl-2H-indazol-2-yl)acetamide	White solid,	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.51 (s, 1H), 7.40 (d, <i>J</i> = 8.9 Hz, 1H), 7.27 – 7.18 (m, 1H), 6.63 – 6.55 (m, 2H), 5.99 (d, <i>J</i> = 1.8 Hz, 1H), 4.82 (s, 2H), 4.80 – 4.72 (m, 1H), 2.43 (s, 3H), 1.59 (d, <i>J</i> = 6.7 Hz, 3H).	384.28 CHIRALP AK ID column, 2cm × 25cm, 5μm, MTBE: IPA. 20mL/min, Rt=1.72 min
Example 343 Method 9 Mixture of Stereoisomers	 2-(6-((1-(5-chloro-4-methylthiazol-2-yl)ethyl)amino)-3-methyl-2H-indazol-2-yl)acetamide	White solid, yield: 18%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.53 (s, 1H), 7.37 (d, <i>J</i> = 9.0 Hz, 1H), 7.26 – 7.21 (m, 1H), 6.59 (dd, <i>J</i> = 9.0, 1.9 Hz, 1H), 6.46 (d, <i>J</i> = 5.6 Hz, 1H), 6.07 (d, <i>J</i> = 2.0 Hz, 1H), 4.82 (s,	364.02

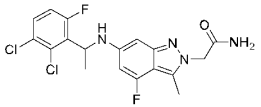
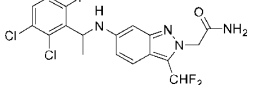
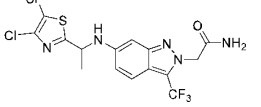
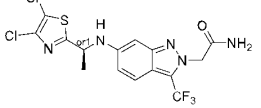
	yl)acetamide		2H), 4.68 (p, $J = 6.8$ Hz, 1H), 2.42 (s, 3H), 2.27 (s, 3H), 1.54 (d, $J = 6.8$ Hz, 3H).	
Example 347 Method 9 single unknown stereoisomer	 rel-(R)-2-(6-((1-(2,4-dichlorothiazol-5-yl)ethyl)amino)-3-methyl-2H-indazol-2-yl)acetamide	White solid, yield: 18%	^1H NMR (400 MHz, DMSO) δ 7.62 – 7.52 (m, 1H), 7.41 (d, $J = 8.8$ Hz, 1H), 7.34 – 7.24 (m, 1H), 6.57 (d, $J = 9.0$ Hz, 1H), 6.00 (s, 1H), 4.85 (s, 1H), 4.68 – 4.62 (m, 1H), 2.44 (s, 2H), 1.55 (d, $J = 6.7$ Hz, 2H).	393.3 Separation Conditions: Apparatus: SFC Thar prep 80; Column: CHIRAL PAK IC 250mm $\times$ 20 mm, 5 μm ; Modifier: 40%MeOH (NH ₄ OH 0.2%); Total Flow: 40g/min, Rt = 5.55 min)
Example 347A Method 9 single unknown stereoisomer	 rel-(R)-2-(6-((1-(2,4-dichlorothiazol-5-yl)ethyl)amino)-3-methyl-2H-indazol-2-yl)acetamide	white solid, yield: 3.54%	^1H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.54 (s, 1H), 7.38 (d, $J = 8.8$ Hz, 1H), 7.25 (s, 1H), 6.54 (m, 1H), 6.46 (d, $J = 4.8$ Hz, 1H), 5.99 (s, 1H), 4.83 (s, 2H), 4.66 – 4.61 (m, 1H), 2.42 (s, 3H), 1.55 (d, $J = 6.6$ Hz, 3H).	393.3 Separation Conditions: Apparatus:

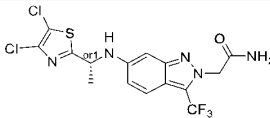
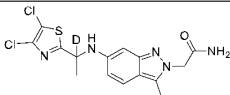
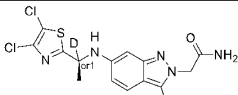
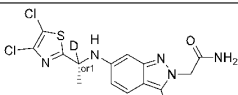
	yl)acetamide			s: SFC Thar prep 80; Column : CHIRAL PAK IC 250mm × 20 mm, 5μm; Modifier : 40%MEO H (NH4OH 0.2%); Total Flow: 40g/min, Rt =4.5 min)
Example 348 Method 9 Mixture of Stereoisomers	 6-((1-(4,5-dichloropyridin-3-yl)ethyl)amino)-8-fluoro-3-(3-hydroxycyclobutyl)quinoxalin-4(3H)-one	White solid, yield: 19.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.66 (s, 1H), 8.53 (s, 1H), 8.14 (s, 1H), 7.27 (d, <i>J</i> = 7.1 Hz, 1H), 6.97 (dd, <i>J</i> = 12.6, 2.6 Hz, 1H), 6.69 (d, <i>J</i> = 2.6 Hz, 1H), 5.24 (d, <i>J</i> = 7.0 Hz, 1H), 4.92 (t, <i>J</i> = 6.9 Hz, 1H), 4.46 – 4.31 (m, 1H), 4.01 – 3.89 (m, 1H), 2.80 – 2.67 (m, 2H), 2.20 – 2.09 (m, 2H), 1.53 (d, <i>J</i> = 6.8 Hz, 3H).	423.01

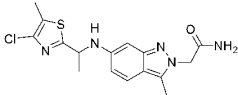
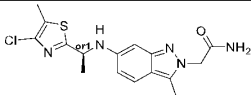
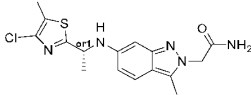
Example 355 Method 9 Mixture of Stereoisomers	 2-(6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-3-(difluoromethyl)-2H-indazol-2-yl)acetamide	White solid, yield: 8.1%	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.59 (d, <i>J</i> = 9.2 Hz, 1H), 7.30 (t, <i>J</i> = 53.6 Hz, 1H), 6.83 (dd, <i>J</i> = 9.2, 2.0 Hz, 1H), 6.36 (d, <i>J</i> = 2.0 Hz, 1H), 5.12 (s, 2H), 4.73 (q, <i>J</i> = 6.8 Hz, 1H), 1.64 (d, <i>J</i> = 6.8 Hz, 3H).	420.4
Example 355A Method 9 single unknown stereoisomer	 rel-(S)-2-(6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-3-(difluoromethyl)-2H-indazol-2-yl)acetamide	white solid, yield: 21.8%	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.59 (d, <i>J</i> = 9.1 Hz, 1H), 7.31 (t, <i>J</i> = 53.7 Hz, 1H), 6.83 (dd, <i>J</i> = 9.2, 1.9 Hz, 1H), 6.36 (d, <i>J</i> = 1.9 Hz, 1H), 5.12 (s, 2H), 4.74 (q, <i>J</i> = 6.8 Hz, 1H), 1.65 (d, <i>J</i> = 6.8 Hz, 3H).	420.06 Separation from 355 , Note: SFC, CHIRAL PAK IF 2cm × 25cm, 5μm Modifier: MtBE(0.1 %DEA):(MeOH:D CM=1:1) =95:5 Rt=3.2 min
Example 355B Method 9 single unknown stereoisomer	 rel-(R)-2-(6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-3-(difluoromethyl)-2H-indazol-2-yl)acetamide	white solid, yield: 23.5%	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.60 (d, <i>J</i> = 9.1 Hz, 1H), 7.31 (t, <i>J</i> = 53.7 Hz, 1H), 6.91 – 6.80 (m, 1H), 6.36 (d, <i>J</i> = 1.9 Hz, 1H), 5.12 (s, 2H), 4.74 (q, <i>J</i> = 6.8 Hz, 1H), 1.65 (d, <i>J</i> = 6.8 Hz, 3H).	420.06 Separation from 355 , Note: SFC CHIRAL PAK IF

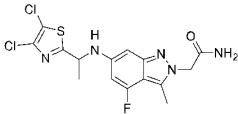
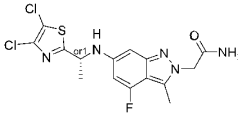
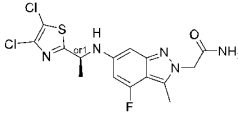
				2cm × 25cm, 5um Modifier : MtBE(0.1 %DEA):(MeOH:D CM=1:1) =95:5 Rt=2.2 min
Example 357 Method 9 Single unknown stereoisomer	 Rel-(S)-2-(7-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-4-methyl-1-oxophthalazin-2(1H)-yl)acetamide	white solid, yield: 24.17 %	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.72 (d, <i>J</i> = 9.2 Hz, 1H), 7.55 (d, <i>J</i> = 6.0 Hz, 1H), 7.45 (s, 1H), 7.25 (d, <i>J</i> = 6.8 Hz, 2H), 7.10 (s, 1H), 5.05 - 4.97 (m, 1H), 4.57 (s, 2H), 2.41 (s, 3H), 1.59 (d, <i>J</i> = 6.4 Hz, 3H).	411.8, 413.9 NOTE: Chiral- IC,5um, 20*250m m, n- Hexane/E tOH, 20 mL/min, RT=10.7 min
Example 358 Method 9 Single unknown stereoisomer	 Rel-(R)-2-(7-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-4-methyl-1-oxophthalazin-2(1H)-yl)acetamide	white solid, yield: 25.83 %	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.72 (d, <i>J</i> = 9.2 Hz, 1H), 7.55 (d, <i>J</i> = 6.0 Hz, 1H), 7.45 (s, 1H), 7.25 (d, <i>J</i> = 6.8 Hz, 2H), 7.10 (s, 1H), 5.05 - 4.97 (m, 1H), 4.57 (s, 2H), 2.41 (s, 3H), 1.59 (d, <i>J</i> = 6.4 Hz, 3H).	411.8, 413.9 NOTE: Chiral- IC,5um, 20*250m m, n- Hexane/E tOH, 20 mL/min, RT=17.5 min
Example 361 Method 9 Mixture of		White solid,	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.60 (s, 1H), 7.34 (d, <i>J</i> = 9.0 Hz,	404.2

stereoisomers	2-(3-chloro-6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-2H-indazol-2-yl)acetamide	yield: 53.6%	¹ H), 7.28 (s, 1H), 6.77 (t, $J = 7.5$ Hz, 2H), 6.23 (s, 1H), 4.90 (s, 2H), 4.80 (t, $J = 6.6$ Hz, 1H), 1.57 (d, $J = 6.7$ Hz, 3H).	
Example 362 Method 9 single unknown stereoisomer	 rel-(S)-2-(6-((1-(5-chloro-4-methylthiazol-2-yl)ethyl)amino)-3-methyl-2H-indazol-2-yl)acetamide	White solid, yield: 35.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.48 (s, 1H), 7.38 (d, $J = 8.9$ Hz, 1H), 7.22 (s, 1H), 6.59 (d, $J = 9.0$ Hz, 1H), 6.42 (d, $J = 5.5$ Hz, 1H), 6.10 (s, 1H), 4.82 (s, 2H), 4.64 (p, $J = 6.1$ Hz, 1H), 2.43 (s, 3H), 2.30 (s, 3H), 1.54 (d, $J = 6.8$ Hz, 3H).	364.1 Note: Chiral separation from 343 , CHIRAL PAK OJ, 5 μ m 3*250mm Ethanol (0.1%DE A) -CO ₂ , 70mL/min, Rt = 0.794 min
Example 363 Method 9 single unknown stereoisomer	 rel-(R)-2-(6-((1-(5-chloro-4-methylthiazol-2-yl)ethyl)amino)-3-methyl-2H-indazol-2-yl)acetamide	White solid, yield: 37.7%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.48 (s, 1H), 7.38 (d, $J = 8.9$ Hz, 1H), 7.22 (s, 1H), 6.59 (d, $J = 9.0$ Hz, 1H), 6.42 (d, $J = 5.5$ Hz, 1H), 6.10 (s, 1H), 4.82 (s, 2H), 4.64 (p, $J = 6.1$ Hz, 1H), 2.43 (s, 3H), 2.30 (s, 3H), 1.54 (d, $J = 6.8$ Hz, 3H).	364.1 Note: Chiral separation from 343 , CHIRAL PAK OJ, 5 μ m 3*250mm Ethanol (0.1%DE A) -CO ₂ , 70mL/min, Rt = 0.675 min

Example 364 Method 9 Mixture of Stereoisomers	 2-(6-((1-(2,3-dichloro-6-fluorophenyl)ethyl)amino)-4-fluoro-3-methyl-2H-indazol-2-yl)acetamide	white solid, yield: 8.13%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.60 – 7.52 (m, 2H), 7.25-7.19 (m, 2H), 6.44 (d, <i>J</i> = 8.0 Hz, 1H), 6.35 (dd, <i>J</i> = 13.5, 1.5 Hz, 1H), 5.73 (d, <i>J</i> = 1.4 Hz, 1H), 5.00 (p, <i>J</i> = 7.2 Hz, 1H), 4.81 (s, 2H), 2.47 (s, 3H), 1.58 (d, <i>J</i> = 6.9 Hz, 3H).	413.25
Example 365 Method 9 Mixture of Stereoisomers	 2-(6-((1-(2,3-dichloro-6-fluorophenyl)ethyl)amino)-3-(difluoromethyl)-2H-indazol-2-yl)acetamide	white solid, yield: 18.6%	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.40 (d, <i>J</i> = 9.0 Hz, 1H), 7.35 – 6.98 (m, 2H), 6.90 (t, <i>J</i> = 9.7 Hz, 1H), 6.72 – 6.63 (m, 1H), 6.17 (s, 1H), 5.11 (q, <i>J</i> = 7.0 Hz, 1H), 4.96 (s, 2H), 1.56 (d, <i>J</i> = 6.9 Hz, 3H).	431.12
Example 366 Method 9 Mixture of Stereoisomers	 2-(6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-3-(trifluoromethyl)-2H-indazol-2-yl)acetamide	White solid, yield: 42.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.64 (s, 1H), 7.49 (s, 1H), 7.33 (s, 1H), 6.92 (s, 2H), 6.38 (s, 1H), 5.05 (s, 2H), 4.91 – 4.70 (m, 1H), 1.58 (d, <i>J</i> = 7.6 Hz, 3H).	438.2
Example 367 Method 9 single unknown stereoisomer	 rel-(S)-2-(6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-3-(trifluoromethyl)-2H-indazol-2-yl)acetamide	White solid, yield: 40.2%	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.59 (d, <i>J</i> = 9.0 Hz, 1H), 6.78 (dd, <i>J</i> = 9.1, 2.1 Hz, 1H), 6.55 (s, 1H), 6.08 (s, 1H), 5.47 (s, 1H), 5.12 (s, 2H), 4.78 (q, <i>J</i> = 6.7 Hz, 1H), 1.72 (d, <i>J</i> = 6.8 Hz, 3H).	438.2 Note: CHIRAL PAK IG, 5um 20*250m m, Ethanol /Hexane, 20mL/min, Rt =

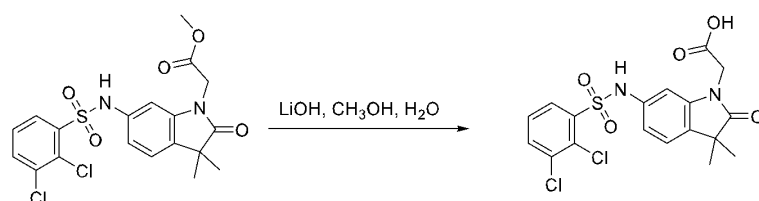
				8.210 min
Example 368 Method 9 single unknown stereoisomer	 rel-(R)-2-(6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-3-(trifluoromethyl)-2H-indazol-2-yl)acetamide	White solid, yield: 39.5%	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.59 (d, J = 9.0 Hz, 1H), 6.78 (dd, J = 9.1, 2.1 Hz, 1H), 6.55 (s, 1H), 6.08 (s, 1H), 5.47 (s, 1H), 5.12 (s, 2H), 4.78 (q, J = 6.7 Hz, 1H), 1.72 (d, J = 6.8 Hz, 3H).	438.2 Note: CHIRAL PAK IG, 5 μ m 20*250m m, Ethanol /Hexane, 20mL/min, Rt = 6.779 min
Example 376 Method 9 Mixture of Stereoisomers	 2-(6-((1-(4,5-dichlorothiazol-2-yl)ethyl-1-d)amino)-3-methyl-2H-indazol-2-yl)acetamide	White solid, yield: 42%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.52 (s, 1H), 7.41 (d, J = 9.0 Hz, 1H), 7.25 (s, 1H), 6.61 (dd, J = 9.0, 2.0 Hz, 1H), 6.55 (s, 1H), 6.15 (d, J = 2.0 Hz, 1H), 4.84 (s, 2H), 2.44 (s, 3H), 1.55 (s, 3H).	385.1
Example 377 Method 9 single unknown stereoisomer	 rel-(S)-2-(6-((1-(4,5-dichlorothiazol-2-yl)ethyl-1-d)amino)-3-methyl-2H-indazol-2-yl)acetamide	White solid, yield: 39.2%	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.40 (d, J = 8.9 Hz, 1H), 6.56 (dd, J = 8.9, 2.0 Hz, 1H), 6.51 (s, 1H), 6.45 (d, J = 2.0 Hz, 1H), 5.44 (s, 1H), 4.92 (s, 2H), 4.26 (s, 1H), 2.55 (s, 3H), 1.68 (s, 3H).	385.1 Note: CHIRAL PAK OJ, 5 μ m 20*250m m, Ethanol /Hexane, 20mL/min, Rt = 7.245 min
Example 378 Method 9 single unknown stereoisomer	 rel-(R)-2-(6-((1-(4,5-dichlorothiazol-2-yl)ethyl-1-d)amino)-3-methyl-2H-indazol-2-yl)acetamide	White solid, yield: 38.1%	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.40 (d, J = 8.9 Hz, 1H), 6.56 (dd, J = 8.9, 2.0 Hz, 1H), 6.51 (s, 1H), 6.45 (d, J =	385.1 Note: CHIRAL PAK OJ, 5 μ m

	yl)ethyl-1-d)amino)-3-methyl-2H-indazol-2-yl)acetamide		2.0 Hz, 1H), 5.44 (s, 1H), 4.92 (s, 2H), 4.26 (s, 1H), 2.55 (s, 3H), 1.68 (s, 3H).	20*250mm, Ethanol /Hexane, 20mL/min, Rt = 6.022 min
Example 379 Method 9 Mixture of Stereoisomers	 2-(6-((1-(4-chloro-5-methylthiazol-2-yl)ethyl)amino)-3-methyl-2H-indazol-2-yl)acetamide	white solid, yield: 69.9%	¹ H NMR (400 MHz, CDCl ₃) δ 7.39 (d, <i>J</i> = 8.8 Hz, 1H), 6.71 (s, 1H), 6.58 (d, <i>J</i> = 8.8 Hz, 1H), 6.47 (s, 1H), 5.40 (s, 1H), 4.95 (s, 2H), 4.84 – 4.76 (m, 1H), 4.36 (s, 1H), 2.56 (s, 3H), 2.31 (s, 3H), 1.68 (d, <i>J</i> = 6.8 Hz, 3H).	364.1
Example 380 Method 9 single unknown stereoisomer	 Rel-(S)-2-(6-((1-(4-chloro-5-methylthiazol-2-yl)ethyl)amino)-3-methyl-2H-indazol-2-yl)acetamide	white solid, yield: 35.8%	¹ H NMR (400 MHz, CDCl ₃) δ 7.38 (d, <i>J</i> = 8.9 Hz, 1H), 6.55 (dd, <i>J</i> = 8.9, 1.8 Hz, 1H), 6.49 (s, 1H), 6.46 (s, 1H), 5.45 (s, 1H), 4.89 (s, 2H), 4.79 (m, 1H), 4.29 (s, 1H), 2.53 (s, 3H), 2.30 (s, 3H), 1.67 (d, <i>J</i> = 6.7 Hz, 3H).	364.2 Note: CHIRAL PAK OJ Sum 3*250mm Ethanol (0.1%DEA) -CO ₂ - 17MIN- 220NM 70 mL/minute Rt=0.786 min
Example 381 Method 9 single unknown stereoisomer	 Rel-(R)-2-(6-((1-(4-chloro-5-methylthiazol-2-yl)ethyl)amino)-3-methyl-2H-indazol-2-yl)acetamide	white solid, yield: 37.7%	¹ H NMR (400 MHz, CDCl ₃) δ 7.38 (d, <i>J</i> = 8.9 Hz, 1H), 6.56 (dd, <i>J</i> = 8.9, 1.8 Hz, 1H), 6.51 (s, 1H), 6.46 (s, 1H), 5.45 (s, 1H), 4.90 (s, 2H),	364.2 Note: CHIRAL PAK OJ Sum 3*250mm

	yl)ethyl)amino)-3-methyl-2H-indazol-2-yl)acetamide		4.79 (d, $J = 6.5$ Hz, 1H), 4.29 (s, 1H), 2.53 (s, 3H), 2.30 (s, 3H), 1.67 (d, $J = 6.7$ Hz, 3H).	Ethanol (0.1%DE A) -CO ₂ -17MIN-220NM 70 mL/minute Rt= 0.668 min
Example 389 Method 9 Mixture of Stereoisomers	 2-(6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-4-fluoro-3-methyl-2H-indazol-2-yl)acetamide	White solid, yield: 35%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.58 (s, 1H), 7.28 (s, 1H), 6.68 (d, $J = 5.2$ Hz, 1H), 6.33 (d, $J = 12.8$ Hz, 1H), 5.99 (s, 1H), 4.86 (s, 2H), 4.78-4.75 (m, 1H), 2.51 (s, 3H), 1.55 (d, $J = 6.4$ Hz, 3H),	402.3
Example 390 Method 9 single unknown stereoisomer	 rel-(R)-2-(6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-4-fluoro-3-methyl-2H-indazol-2-yl)acetamide	White solid	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.59 (s, 1H), 7.29 (s, 1H), 6.68 (d, $J = 5.7$ Hz, 1H), 6.34 (d, $J = 13.1$ Hz, 1H), 5.99 (s, 1H), 4.86 (s, 2H), 4.76 (p, $J = 6.4$ Hz, 1H), 2.51 (s, 3H), 1.55 (d, $J = 6.7$ Hz, 3H).	402.3 Note: CHIRAL Cellulose SB, 2cm*25cm, 5um, MeOH/D CM, MtBE, 20mL/min, Rt = 2.2 min
Example 391 Method 9 single unknown stereoisomer	 rel-(S)-2-(6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-4-fluoro-3-methyl-2H-indazol-2-yl)acetamide	White solid	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.59 (s, 1H), 7.29 (s, 1H), 6.68 (d, $J = 5.7$ Hz, 1H), 6.34 (d, $J = 13.1$ Hz, 1H), 5.99 (s, 1H), 4.86 (s, 2H), 4.76 (p, $J = 6.4$ Hz, 1H), 2.51 (s, 3H), 1.55	402.3 Note: CHIRAL Cellulose SB, 2cm*25cm, 5um, MeOH/D

	yl)acetamide		(d, $J = 6.7$ Hz, 3H).	CM, MtBE, 20mL/min, Rt = 3.03 min

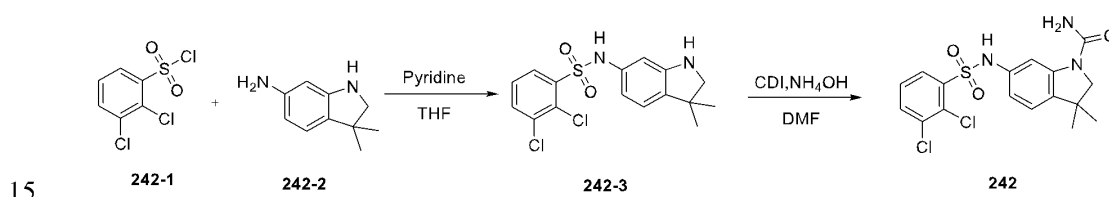
Preparation of 2-[6-[(2,3-dichlorophenyl)sulfonylamino]-3,3-dimethyl-2-oxo-indolin-1-yl]acetic acid (241**)**



To a solution of methyl 2-[6-[(2,3-dichlorophenyl)sulfonylamino]-3,3-dimethyl-2-oxo-indolin-1-yl]acetate (1.00 eq, 40 mg, 0.088 mmol) in methanol (1 mL) was added lithium hydroxide (2.00 eq, 4.2 mg, 0.175 mmol) in water (0.2 mL) and then stirred at RT for 2 h. The reaction was acidified with 1N HCl to pH ~5 and concentrated under vacuum. The residue was purified by Prep-HPLC to afford the desired product **241** (2.8 mg, 0.0062 mmol, 7.08% yield) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.05 (dd, $J = 7.9, 1.6$ Hz, 1H), 7.88 (dd, $J = 8.1, 1.5$ Hz, 1H), 7.52 (t, $J = 8.0$ Hz, 1H), 7.18 (d, $J = 8.0$ Hz, 1H), 6.69 (dd, $J = 8.0, 1.9$ Hz, 1H), 6.64 (d, $J = 1.9$ Hz, 1H), 4.25 (s, 2H), 1.19 (s, 6H). Mass (m/z): 443.3 $[\text{M}+\text{H}]^+$.

Preparation of

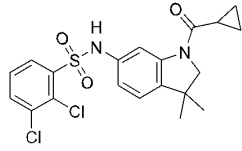
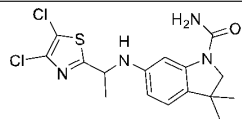
6-((2,3-dichlorophenyl)sulfonamido)-3,3-dimethylindoline-1-carboxamide (242**) Method 10**

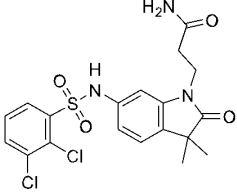
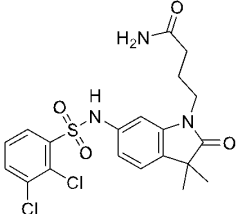
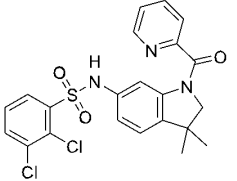


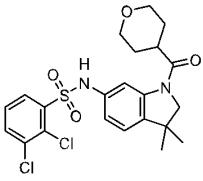
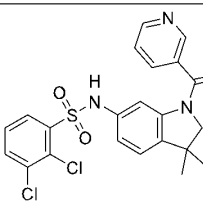
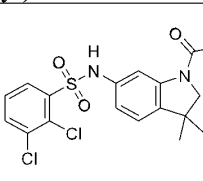
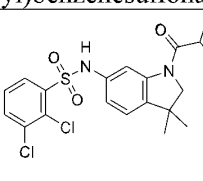
Step 1: To a solution of 2,3-dichlorobenzenesulfonyl chloride **242-1** (1.00 eq, 454 mg, 1.849 mmol) and Pyridine (3.00 eq, 438 mg, 5.548 mmol) in THF (10 mL) was added 3,3-dimethylindolin-6-amine **242-2** (1.00 eq, 300 mg, 1.85 mmol) at 25 °C. The mixture was stirred at 25 °C for 12 h. Added H₂O (20 mL) and extracted with EtOAc. The combined organic layers were washed with HCl solution (1mol/L) (25 mL x 3) and dried over Na₂SO₄,

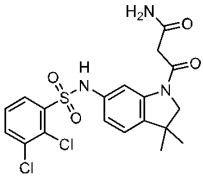
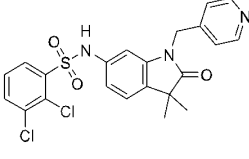
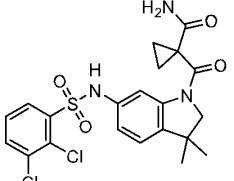
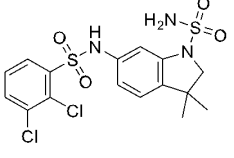
filtered, and concentrated in vacuo. The crude product was purified by silica column to afford 2,3-dichloro-N-(2-oxoindolin-6-yl)benzenesulfonamide **242-3** (380 mg, 0.97 mmol, 52.6% yield) as a white solid. Mass(m/z): 371/373 [M+H]⁺.

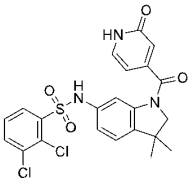
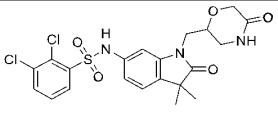
- Step 2:** To a solution of 2,3-dichloro-N-(3,3-dimethylindolin-6-yl)benzenesulfonamide **242-3** (1.00 eq, 50 mg, 0.135 mmol) in DMF (10mL) was added 1,1'-Carbonyldiimidazole (3.00 eq, 66 mg, 0.404 mmol). The reaction was stirred overnight at 25 °C. Ammonium hydroxide (5.00 eq, 24 mg, 0.673 mmol) was added and the mixture was stirred 5 min at 25 °C. The mixture was then extracted by EA (25 mL x 3). The combined organic layers were washed with brine (15 mL x 3), dried over Na₂SO₄ and concentrated to give the crude product, which was purified by prep-HPLC to give the desired product **242** (5.6 mg, 0.0134 mmol, 9.94% yield) as a white solid. Mass(m/z): 414.1/416.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.61 (s, 1H), 7.99 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.90 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.66 (d, *J* = 2.0 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.59 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.24 (s, 2H), 3.57 (s, 2H), 1.18 (s, 6H).
- Compounds **243**, **276**, **279-281**, **284-285**, **295-296**, **299**, **309**, **313**, **319**, **326**, and **333** were synthesized using a method similar to that used for Compound **242**.

Example (Compound) No. Method	Structure and Name	Appearance and Yield	¹ H NMR Data	MS (m/z)
Example 243 Method 10	 2,3-dichloro-N-(1-(cyclopropanecarbonyl)-3,3-dimethylindolin-6-yl)benzenesulfonamide	white solid, yield: 38.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.70 (s, 1H), 7.99 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.90 (dd, <i>J</i> = 8.0, 1.6 Hz, 2H), 7.53 (t, <i>J</i> = 8.0 Hz, 1H), 7.08 (d, <i>J</i> = 8.0 Hz, 1H), 6.74 (dd, <i>J</i> = 8.0, 2.0 Hz, 1H), 3.98 (s, 2H), 1.92 - 1.80 (m, 1H), 1.23 (s, 6H), 0.95 - 0.72 (m, 4H).	439.0/41.0
Example 276 Method 10 Mixture of Stereoisomers	 6-((1-(4,5-dichlorothiazol-2-yl)-1-oxo-2-aminopropan-2-yl)amino)-3,3-dimethylindolin-2-one	white solid, yield: 15.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.30 (d, <i>J</i> = 2.0 Hz, 1H), 6.84 (d, <i>J</i> = 8.0 Hz, 1H), 6.42 (d, <i>J</i> = 5.6 Hz, 1H), 6.18 (s, 2H), 6.06 (dd, <i>J</i> = 8.0, 2.0 Hz,	385.0/387.0

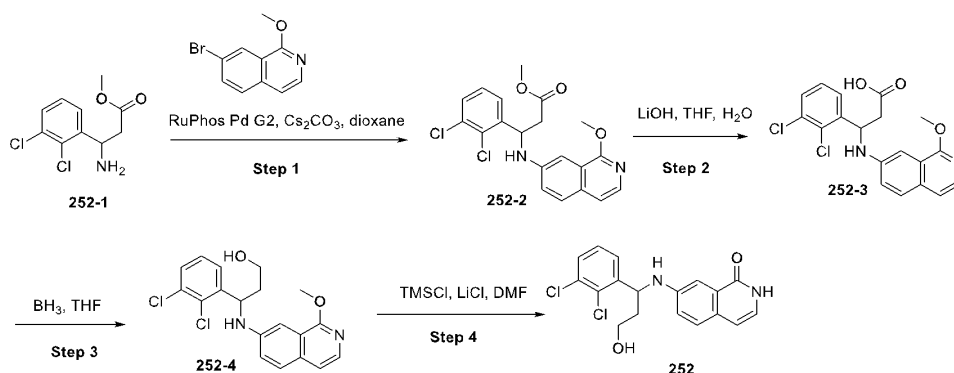
	yl)ethyl)amino)-3,3-dimethylindoline-1-carboxamide		¹ H), 4.59 (p, <i>J</i> = 6.8 Hz, 1H), 3.56 (s, 2H), 1.49 (d, <i>J</i> = 6.8 Hz, 3H), 1.19 (s, 6H).	
Example 279 Method 10	 3-((6-((2,3-dichlorophenyl)sulfonamido)-3,3-dimethyl-2-oxoindolin-1-yl)propanamide	white solid, yield: 12.3 %	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.14 (s, 1H), 8.08 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.85 (d, <i>J</i> = 8.0 Hz, 1H), 7.49 (t, <i>J</i> = 8.0 Hz, 1H), 7.40 (s, 1H), 7.10 – 7.06 (m, 1H), 6.88 (s, 1H), 6.73 (s, 1H), 6.64 (dt, <i>J</i> = 4.0, 2.0 Hz, 1H), 3.73 (dd, <i>J</i> = 8.4, 6.4 Hz, 2H), 2.28 (t, <i>J</i> = 7.2 Hz, 2H), 1.15 (d, <i>J</i> = 4.8 Hz, 6H).	456.2/458.2.
Example 280 Method 10	 4-((6-((2,3-dichlorophenyl)sulfonamido)-3,3-dimethyl-2-oxoindolin-1-yl)butanamide	white solid, yield: 21.4%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.03 (s, 1H), 8.13 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.88 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.53 (t, <i>J</i> = 8.0 Hz, 1H), 7.29 (s, 1H), 7.14 (d, <i>J</i> = 8.0 Hz, 1H), 6.81 – 6.74 (m, 1H), 6.72 (d, <i>J</i> = 2.0 Hz, 1H), 6.66 (dd, <i>J</i> = 8.0, 2.0 Hz, 1H), 3.55 (t, <i>J</i> = 7.2 Hz, 2H), 2.02 (q, <i>J</i> = 8.0 Hz, 2H), 1.67 (p, <i>J</i> = 7.2 Hz, 2H), 1.17 (s, 6H).	470.0/472.0
Example 281 Method 10	 2,3-dichloro-N-(3,3-dimethyl-1-picolinoylindolin-6-yl)benzenesulfonamide	Light-yellow solid, yield: 6.5%	¹ H NMR (400 MHz, CDCl ₃) δ 8.65 (s, 1H), 8.19-8.14 (m, 1H), 7.97 (s, 3H), 7.63 (m, 2H), 7.30 (m, 1H), 7.04-7.02 (m, 1H), 6.88-6.86 (m, 1H), 3.83 (s, 2H), 1.15 (s, 6H).	476.0

Example 284 Method 10	 2,3-dichloro-N-[3,3-dimethyl-1-(tetrahydropyran-4-carbonyl)indolin-6-yl]benzenesulfonamide	white solid, yield: 39.3%	^1H NMR (400 MHz, DMSO- d_6) δ 10.68 (s, 1H), 8.01 (dd, J = 8.0, 1.5 Hz, 1H), 7.99 – 7.94 (m, 1H), 7.90 (dd, J = 8.1, 1.5 Hz, 1H), 7.53 (t, J = 8.0 Hz, 1H), 7.08 (d, J = 8.1 Hz, 1H), 6.77 (dd, J = 8.1, 2.1 Hz, 1H), 4.00 – 3.78 (m, 4H), 3.45 – 3.35 (m, 2H), 2.86 – 2.71 (m, 1H), 1.72 – 1.55 (m, 4H), 1.20 (s, 6H).	483.08
Example 285 Method 10	 2,3-dichloro-N-(3,3-dimethyl-1-nicotinoylindolin-6-yl)benzenesulfonamide	white solid, yield: 7.1%	^1H NMR (400 MHz, CDCl_3) δ 8.76-8.72 (m, 2H), 8.51 (m, 3H), 7.79-7.77 (m, 1H), 7.61 (m, 1H), 7.58 (m, 1H), 7.45-7.13 (m, 1H), 6.94 (s, 1H), 3.81 (s, 2H), 1.27 (s, 6H).	476.0
Example 295 Method 10	 2,3-dichloro-N-(3,3-dimethyl-1-(1-methyl-1H-pyrazole-3-carbonyl)indolin-6-yl)benzenesulfonamide	white solid, yield: 11.7%	^1H NMR (400 MHz, Methanol- d_4) δ 7.97 (s, 2H), 7.65 - 7.64 (m, 1H), 7.63 (s, 1H), 7.33 - 7.29 (m, 1H), 6.99 - 6.97 (m, 1H), 6.81-6.67 (m, 2H), 4.20 (s, 2H), 3.87 (s, 3H), 1.16 (s, 6H).	479.0
Example 296 Method 10	 2,3-dichloro-N-(1-isonicotinoyl-3,3-dimethylindolin-6-yl)benzenesulfonamide	yellow solid, yield: 10.9%	^1H NMR (400 MHz, DMSO- d_6) δ 10.82 (s, 1H), 8.72 (d, J = 5.1 Hz, 2H), 8.18 – 7.88 (m, 3H), 7.62 – 7.53 (m, 3H), 7.15 (d, J = 8.1 Hz, 1H), 6.87 (d, J = 8.1 Hz, 1H), 3.65 (s, 2H), 1.17 (s, 6H).	476.0

Example 299 Method 10	 3-(6-((2,3-dichlorophenyl)sulfonamido)-3,3-dimethylindolin-1-yl)-3-oxopropanamide	white solid, yield: 10.6%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.70 (s, 1H), 8.01 (dd, <i>J</i> = 8.0, 1.5 Hz, 1H), 7.92 (dd, <i>J</i> = 7.8, 1.6 Hz, 2H), 7.55 (t, <i>J</i> = 8.0 Hz, 1H), 7.51 (s, 1H), 7.09 (d, <i>J</i> = 8.1 Hz, 2H), 6.77 (dd, <i>J</i> = 8.1, 2.1 Hz, 1H), 3.82 (s, 2H), 3.36 (s, 2H), 1.20 (s, 6H).	456
Example 309 Method 10	 2,3-dichloro-N-(3,3-dimethyl-2-oxo-1-(pyridin-4-ylmethyl)indolin-6-yl)benzenesulfonamide	White solid, yield: 3.3%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.50 – 8.47 (m, 2H), 7.85 – 7.79 (m, 1H), 7.74 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.38 – 7.32 (m, 1H), 7.18 (t, <i>J</i> = 7.4 Hz, 1H), 7.09 (dd, <i>J</i> = 4.6, 1.6 Hz, 2H), 6.66 (dd, <i>J</i> = 7.0, 5.4 Hz, 1H), 6.49 – 6.45 (m, 1H), 4.79 (s, 2H), 1.23 (s, 6H).	475.9
Example 313 Method 10	 1-(6-((2,3-dichlorophenyl)sulfonamido)-3,3-dimethylindoline-1-carbonyl)cyclopropane-1-carboxamide	White solid, yield: 46.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.72 (br s, 1H), 8.02 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.92 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.89 – 7.81 (m, 1H), 7.56 (t, <i>J</i> = 8.0 Hz, 1H), 7.17 (br s, 2H), 7.08 (d, <i>J</i> = 8.0 Hz, 1H), 6.78 (dd, <i>J</i> = 8.0, 2.0 Hz, 1H), 3.76 (s, 2H), 1.29 – 1.22 (m, 4H), 1.19 (s, 6H).	482.3
Example 319 Method 10	 6-((2,3-dichlorophenyl)sulfonamido)-3,3-dimethylindoline-1-sulfonamide	white solid, yield: 7.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.70 (s, 1H), 8.02 (dd, <i>J</i> = 8.0, 1.4 Hz, 1H), 7.92 (dd, <i>J</i> = 8.0, 1.4 Hz, 1H), 7.55 (t, <i>J</i> = 8.0 Hz, 1H), 7.25 (s, 2H), 7.18 (d, <i>J</i> = 1.9 Hz, 1H), 7.03 (d, <i>J</i> = 8.1 Hz, 1H), 6.64 (dd, <i>J</i> = 8.1, 1.9 Hz, 1H), 3.51 (s, 2H), 1.20 (s, 6H).	450

Example 326 Method 10	 2,3-dichloro-<i>N</i>-(3,3-dimethyl-1-(2-oxo-1,2-dihydropyridine-4-carbonyl)indolin-6-yl)benzenesulfonamide	yellow solid, yield: 0.7%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.79 (s, 1H), 7.94 (dd, <i>J</i> = 8.0, 1.4 Hz, 3H), 7.58 (t, <i>J</i> = 8.0 Hz, 1H), 7.13 (d, <i>J</i> = 8.0 Hz, 1H), 6.83 (s, 1H), 6.49 (s, 2H), 6.25 (s, 2H), 3.66 (s, 2H), 1.17 (s, 6H).	492
Example 333 Method 10	 2,3-dichloro-<i>N</i>-(3,3-dimethyl-2-oxo-1-((5-oxomorpholin-2-yl)methyl)indolin-6-yl)benzenesulfonamide	White solid, yield: 6.8%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.82 (s, 1H), 8.09 (dd, <i>J</i> = 8.0, 1.4 Hz, 1H), 8.01 (d, <i>J</i> = 3.6 Hz, 1H), 7.93 (dd, <i>J</i> = 8.2, 1.4 Hz, 1H), 7.55 (t, <i>J</i> = 8.0 Hz, 1H), 7.19 (d, <i>J</i> = 8.0 Hz, 1H), 6.82 (d, <i>J</i> = 1.6 Hz, 1H), 6.73 (dd, <i>J</i> = 8.0, 1.8 Hz, 1H), 3.93 (d, <i>J</i> = 5.8 Hz, 2H), 3.83 (d, <i>J</i> = 4.2 Hz, 1H), 3.76 – 3.66 (m, 2H), 3.18 (m, 1H), 3.12 – 3.05 (m, 1H), 1.19 (s, 6H).	498.1

Preparation of 7-((1-(2,3-dichlorophenyl)-3-hydroxypropyl)amino)isoquinolin-1(2H)-one (252) (mixture of stereoisomers)



Step 1: A mixture of 3-amino-3-(2,3-dichlorophenyl)propanoate **252-1** (400 mg, 1.6122 mmol), 7-bromo-1-methoxy-1,2-dihydroisoquinoline (387 mg, 1.61 mmol), RuPhos Pd G₂ (250 mg, 0.32 mmol) and Cs₂CO₃ (1576 mg, 4.84 mmol) in 1,4-dioxane (10 mL) was stirred

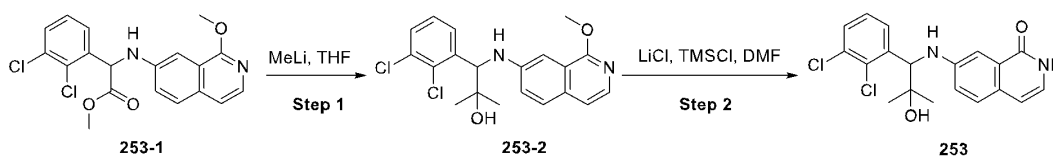
under N₂ for 16 hour at 100 °C. The reaction mixture was diluted with water (50 mL) after the reaction was completed, and extracted with ethyl acetate (50 mL). The organic layers were combined, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product that was purified through column chromatography on silica gel (EA:PE=1:1) to give compound **252-2** (300 mg, 45.6% yield) as oil .MS (m/z) 405.1 [M+H]⁺.

Step 2: A mixture of **252-2** (300 mg, 0.74 mmol) and LiOH (156 mg, 3.71 mmol) in THF: H₂O (5 mL) was stirred under nitrogen at 25 °C for 2 h. The reaction mixture was extracted with EA (30 mL). Organic layers were combined, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product that was purified through column chromatography on silica gel (MeOH:CH₂Cl₂=1:10) to give 3-(2,3-dichlorophenyl)-3-((1-methoxyisoquinolin-7-yl)amino)propanoic acid (200 mg, 68.9% yield) as oil. MS (ESI) m/z 391.1 [M+H]⁺.

Step 3: A mixture of 3-(2,3-dichlorophenyl)-3-((1-methoxyisoquinolin-7-yl)amino)propanoic acid (200 mg, 0.5128 mmol), BH₃ in THF (5 mL) was stirred for 16 hour at 50 °C. The reaction was quenched with water and extracted with EA (50 mL). The organic layers were combined and concentrated under vacuum to give compound **252-3** (110 mg, 56.9% yield) as oil. MS (m/z) 377.1 [M+H]⁺.

Step 4: A mixture solution of **252-3** (110 mg, 0.28 mmol), TMSCl (61 mg, 0.5648 mmol), LiCl (24 mg, 0.5714 mmol) in DMF (3 mL) was stirred at 80 °C for 18 h. The reaction was diluted with water (20 mL) and extracted three times with EA (30 mL). The organic layers were combined, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product that was purified by prep-HPLC (column-Gemini-C18 150 x 21.2 mm, 5 µm; Mobile phase: ACN-H₂O (0.1%TFA), 30%-70%) to afford the desired product (31.6 mg) as a white solid. MS (m/z) 362.9 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.83 (d, *J* = 5.0 Hz, 1H), 7.45 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.39 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.32 – 7.23 (m, 2H), 6.99 – 6.94 (m, 2H), 6.79 – 6.73 (m, 2H), 6.27 (d, *J* = 7.0 Hz, 1H), 4.96 (dd, *J* = 13.0, 7.6 Hz, 1H), 4.64 (t, *J* = 5.0 Hz, 1H), 3.56 (ddd, *J* = 14.8, 9.4, 5.5 Hz, 2H), 1.91 – 1.73 (m, 2H).

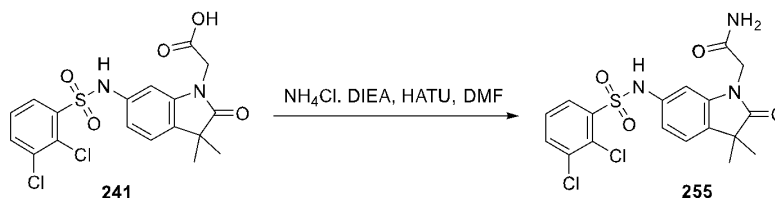
Preparation of 7-((1-(2,3-dichlorophenyl)-2-hydroxy-2-methylpropyl)amino)isoquinolin-1(2H)-one (253) (mixture of stereoisomers)



Step 1: A mixture of **253-1** (180 mg, 1.035 mmol) and MeLi (0.9 mL) in THF (5 mL) was stirred under nitrogen at -78 °C for 30 mins. The reaction was quenched with water (20 mL) and extracted with EA (30 mL), Organic layer were combined, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product that was purified through
 5 column chromatography on silica gel (MeOH: CH₂Cl₂=1:10) to give the **253-2** (50 mg, 27.7% yield) as a yellow solid. MS (m/z) 391.1 [M+H]⁺.

Step 2: A mixture of **253-2** (50 mg, 0.13 mmol), TMSCl (28 mg, 0.26 mmol), and LiCl (11 mg, 0.26 mmol) in DMF (2 mL) was stirred at 80 °C for 18 h. The reaction was diluted with water (20 mL), and extracted three times with EA (30 mL). Organic layers were combined,
 10 dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a crude product that was purified by prep-HPLC (column-Gemini-C18 150 x 21.2 mm, 5 um; Mobile phase: ACN-H₂O (0.1%FA), 40%-60%) to afford the desired product **253** (10.5 mg) as a yellow solid.
¹H NMR (400 MHz, DMSO-*d*₆) δ 10.79 (d, *J* = 5.6 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.44 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.29 – 7.21 (m, 2H), 7.13 (d, *J* = 2.0 Hz, 1H), 7.09 (dd, *J* = 8.6,
 15 2.5 Hz, 1H), 6.75 (dd, *J* = 7.0, 5.8 Hz, 1H), 6.45 (d, *J* = 8.8 Hz, 1H), 6.26 (d, *J* = 6.6 Hz, 1H), 4.82 (s, 1H), 4.79 (s, 1H), 1.31 (s, 3H), 1.02 (s, 3H). MS (m/z) 377.0 [M+H]⁺.

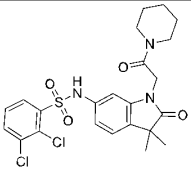
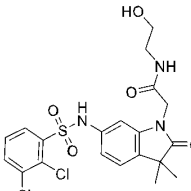
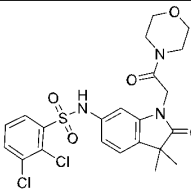
Preparation of 2-[6-[(2,3-dichlorophenyl)sulfonylamino]-3,3-dimethyl-2-oxo-indolin-1-yl]acetamide (255**) Method 11**



20 A mixture of **241** (1.00 eq, 120 mg, 0.27 mmol), ammonium chloride (6.00 eq, 87 mg, 1.62 mmol), N-ethyl-N-isopropyl-propan-2-amine (10.0 eq, 350 mg, 2.71 mmol) and HATU (2.00 eq, 206 mg, 0.541 mmol) in DMF (1 mL) was stirred overnight at room temperature. The reaction was diluted with water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under vacuum. The residue was purified by Prep-HPLC
 25 to afford **255** as a yellow solid (7.3 mg, 0.016 mmol, 5.97% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.83 (s, 1H), 8.06 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.93 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.65 (s, 1H), 7.57 (t, *J* = 8.1 Hz, 1H), 7.24 (s, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 6.70 (dd, *J* = 8.0, 2.0

Hz, 1H), 6.61 (d, $J = 1.9$ Hz, 1H), 4.15 (s, 2H), 1.20 (s, 6H). Mass (m/z): 442.3 [M+H]⁺.

Compounds **286-287**, and **291** were synthesized using a method like that used for Compound **255**.

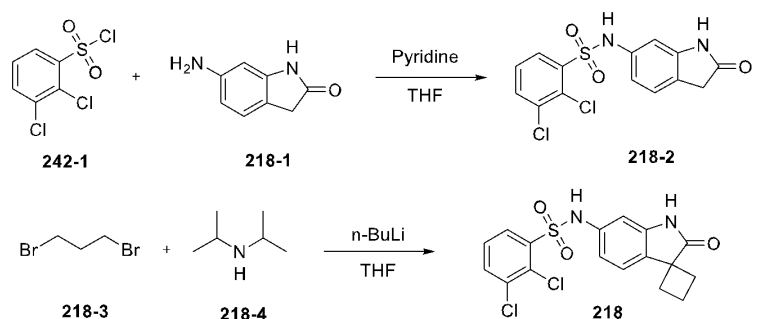
Example (Compound) No. Method	Structure and Name	Appearance and Yield	¹ H NMR Data	MS (m/z) [M+H] ⁺
Example 286 Method 11	 2,3-dichloro-N-(3,3-dimethyl-2-oxo-1-(2-oxo-2-(piperidin-1-yl)ethyl)indolin-6-yl)benzenesulfonamide	white solid, yield: 43.4%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.79 (s, 1H), 8.03 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.94 (dd, $J = 8.2, 1.4$ Hz, 1H), 7.54 (t, $J = 8.2$ Hz, 1H), 7.19 (d, $J = 8.0$ Hz, 1H), 6.69 (dd, $J = 8.0, 2.0$ Hz, 1H), 6.56 (d, $J = 1.8$ Hz, 1H), 4.45 (s, 2H), 3.48 (s, 2H), 3.42 – 3.36 (m, 2H), 1.62 (s, 2H), 1.55 (s, 2H), 1.43 (s, 2H), 1.22 (s, 6H)	509.9
Example 287 Method 11	 2-(6-((2,3-dichlorophenyl)sulfonamido)-3,3-dimethyl-2-oxoindolin-1-yl)-N-(2-hydroxyethyl)acetamide	white solid, yield: 15.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.81 (s, 1H), 8.22 (t, $J = 5.6$ Hz, 1H), 8.05 (dd, $J = 8.0, 1.4$ Hz, 1H), 7.94 (dd, $J = 8.2, 1.4$ Hz, 1H), 7.56 (d, $J = 8.2$ Hz, 1H), 7.18 (d, $J = 8.0$ Hz, 1H), 6.70 (dd, $J = 8.0, 2.0$ Hz, 1H), 6.58 (d, $J = 1.8$ Hz, 1H), 4.19 (s, 2H), 3.46 – 3.41 (m, 1H), 3.15 (d, $J = 5.8$ Hz, 2H), 1.20 (s, 6H).	485.9
Example 291 Method 11		white solid, yield: 24.3%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.77 (s, 1H), 8.05 (dd, $J = 8.0, 1.4$ Hz, 1H), 7.94 (dd, $J = 8.2, 1.6$ Hz, 1H), 7.54 (t, $J = 8.0$	511.9

	2,3-dichloro-N-(3,3-dimethyl-1-(2-morpholino-2-oxoethyl)-2-oxoindolin-6-yl)benzenesulfonamide		Hz, 1H), 7.19 (d, $J = 8.0$ Hz, 1H), 6.68 (dd, $J = 8.0$, 2.0 Hz, 1H), 6.58 (d, $J = 1.8$ Hz, 1H), 4.52 (s, 2H), 3.65 (d, $J = 4.2$ Hz, 2H), 3.58 (d, $J = 4.4$ Hz, 4H), 3.42 (d, $J = 4.8$ Hz, 2H), 1.22 (s 6H).	
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Preparation of

2,3-dichloro-N-(2'-oxospiro[cyclobutane-1,3'-indolin]-6'-yl)benzenesulfonamide (**218**)

Method 13

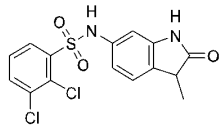


- 5 **Step 1:** To a solution of 2,3-dichlorobenzenesulfonyl chloride **242-1** (1.00 eq, 300 mg, 1.22 mmol) and Pyridine (3.00 eq, 0.29 mL, 3.67 mmol) in THF (10mL) was added 6-aminoindolin-2-one **218-1** (1.00 eq, 181 mg, 1.22 mmol) at 25 °C. The mixture was stirred at 25 °C for 12 h. H₂O (20 mL) was added, and the organic phase was extracted with EtOAc. The combined organic layers were washed with an HCl solution (1mol/L) (25 mL x 3) and dried over Na₂SO₄,
 10 filtered, and concentrated in vacuo. The crude product was purified by silica column to afford **218-2** (415 mg, 1.07 mmol, 87.5% yield) as a red solid. Mass(m/z): 357/359 [M+H]⁺.

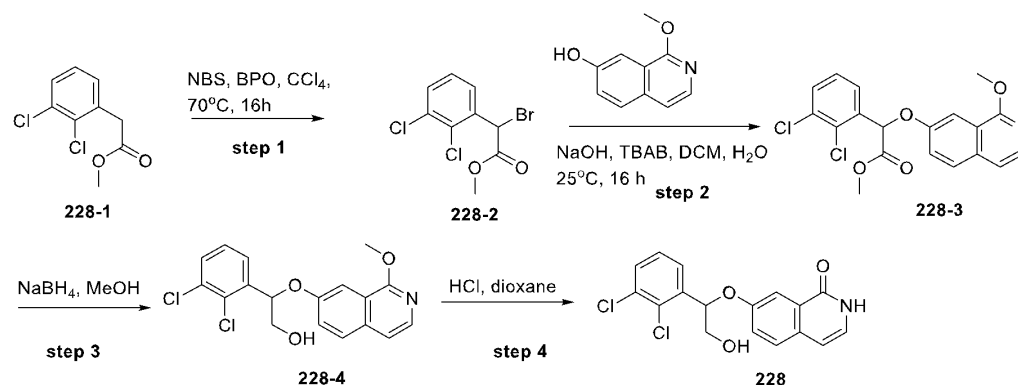
- Step 2:** *n*-BuLi (4.00 eq, 0.5 mL, 1.12 mmol) was added dropwise to a stirred and cooled (-70 °C) suspension of **218-2** (1.00 eq, 100 mg, 0.28 mmol) and N-isopropylpropan-2-amine **218-4** (4 eq, 113 mg, 1.12 mmol) in dry THF (20mL) under Ar₂. During addition the temperature
 15 was maintained below -70 °C. After addition was completed, the temperature was allowed to warm to 0 °C, then a solution of 1,3-dibromopropane **218-3** (1.1 eq, 62 mg, 0.308 mmol) in dry THF (10 mL) was added dropwise while maintaining a temperature of below -70 °C. After addition was completed, the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated to a smaller volume under reduced pressure. The residue

was diluted with EtOAc (20 mL) and brine (20 mL). The biphasic mixture was then stirred vigorously. The PH was adjusted to 5 by slowly adding 4M aqueous HCl. The biphasic system was filtered through a glass filter in order to remove the solids which appeared in the biphasic system. The solids were rinsed with EtOAc, collected and dried on the air to give a first batch of **218** (1.7 mg, 0.0042 mmol, 1.51% yield) as a white solid. Mass (m/z): 397.2/399.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.97 (s, 1H), 8.34 (s, 1H), 7.94 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 6.61 - 6.46 (m, 2H), 2.31 (d, *J* = 7.2 Hz, 2H), 2.19 - 2.11 (m, 2H), 2.08 - 1.98 (m, 2H).

235 was synthesized using a similar method to that used for **218**.

Example (Compound) No. Method	Structure and Name	Appearance and Yield	¹ H NMR Data	MS (m/z)
Example 235 Method 13 Mixture of Stereoisomers	 2,3-dichloro-N-(3-methyl-2-oxoindolin-6-yl)benzenesulfonamide	white solid, yield: 2.7%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.72 (s, 1H), 10.25 (s, 1H), 7.99 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.92 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.54 (t, <i>J</i> = 8.0 Hz, 1H), 7.07 (d, <i>J</i> = 8.0 Hz, 1H), 6.71 - 6.59 (m, 2H), 3.27 (t, <i>J</i> = 7.6 Hz, 1H), 1.22 (d, <i>J</i> = 7.6 Hz, 3H).	371.0/373.0

10 Preparation of 7-(1-(2,3-dichlorophenyl)-2-hydroxyethoxy)isoquinolin-1(2H)-one (228) (mixture of stereoisomers)



Step 1: To a stirred solution of **228-1** (2.00 g, 9.10 mmol), BPO (0.22 g, 0.91 mmol) in CCl_4 (20 mL) was added NBS (1.62 g, 9.10 mmol). The mixture was stirred at 70°C for 16hrs.

LCMS showed the reaction was complete. The mixture was filtered. The filtrate was

concentrated to give **228-2** (2.3 g, 84.4%) as yellow oil.

Step 2: To a solution of **228-2** (90 mg, 0.30 mmol) and 1-methoxyisoquinolin-7-ol (53 mg, 0.30 mmol), TBAB (9.7 mg, 0.03 mmol) in DCM (5 mL) was added a solution of NaOH (13 mg, 0.33 mmol) in H_2O (0.5 mL). The mixture was stirred at 25°C for 16 hrs. The mixture was treated with H_2O (10 mL) and extracted with DCM (10 mLx3). The combined organic layers

were washed with brine (10 mL), dried over Na_2SO_4 , and concentrated. The residue was purified by prep-TLC (PE/EA=3:1) to give **228-3** (80 mg, 67.5%) as a yellow solid.

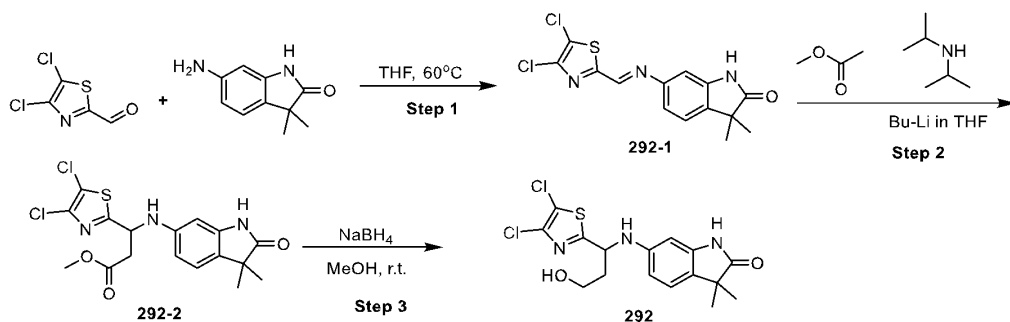
Step 3: To a solution of **228-3** (70 mg, 0.18 mmol) in MeOH (5 mL) was added NaBH_4 (20 mg, 0.54 mmol). The mixture was stirred at 25°C for 4 hrs. The mixture was quenched with H_2O (20 mL) and extracted with EA (20 mLx3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , and concentrated. The residue was purified by prep-TLC (PE/EA=1:1) to **228-4** (48 mg, 73.6%) as a white solid.

Step 4: A solution of **228-4** (40 mg, 0.11 mmol) in dioxane (2 mL) and 6N HCl (2 mL) was stirred at 100 °C for 4 hrs. LCMS showed the reaction was completed. The mixture was

concentrated and the residue was purified by prep-HPLC (sunfire 5 μm 19-150 mm, Mobile

Phase: MeCN- H_2O (0.1% FA), Gradient: 25-75-8 min, Flow Rate: 20 mL/min) to give **228** (26 mg, 67.4%) as a white solid. $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 11.17 (d, J = 4.8 Hz, 1H), 7.63-7.54 (m, 2H), 7.46-7.40 (m, 2H), 7.37-7.30 (m, 2H), 7.01 (dd, J = 6.8 Hz, 5.6 Hz, 1H), 6.47 (d, J = 6.8 Hz, 1H), 5.71 (t, J = 4.8 Hz, 1H), 5.37 (t, J = 6.0 Hz, 1H), 3.75 (t, J = 5.2 Hz, 2H). Mass (m/z): 349.9 $[\text{M} + \text{H}]^+$.

Preparation of 6-((1-(4,5-dichlorothiazol-2-yl)-3-hydroxypropyl)amino)-3,3-

dimethylindolin-2-one (292) (mixture of stereoisomers) Method 14

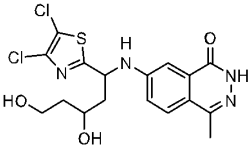
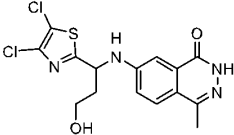
Step 1: To a solution of 4,5-dichlorothiazole-2-carbaldehyde (1.00 eq, 500 mg, 2.75 mmol) in THF (10 mL) was added 6-amino-3,3-dimethyl-indolin-2-one (1.00 eq, 484 mg, 2.75 mmol).

- 5 The reaction mixture was heated to 60 °C. After reaction completed, the reaction solution was concentrated in vacuo to afford **292-1** (880 mg, 2.59 mmol, 94.2% yield) as a yellow solid.

Step 2: At -40°C, n-BuLi in n-hexane (2.4 M, 10.0 eq, 7.3 mL, 17.8 mmol) was added to a solution of diisopropylamine (10.0 eq, 2.5 mL, 17.8 mmol) in distilled THF (30 mL). After stirring for 1 h, the solution was cooled to -78 °C and dry methyl acetate (10.0 eq, 1.4 mL, 17.8 mmol) was slowly added. After stirring for 1 hour, a solution of **292-1** (1.00 eq, 604 mg, 1.78 mmol) in distilled THF (15.0 mL) was added to the reaction mixture. The reaction mixture was stirred at -78 °C for 10 minutes and then the reaction was quenched by adding NH₄Cl solution at the same temperature. The reaction mixture was extracted with EA and concentrated in vacuo. The residue was subjected to flash column chromatography (EA: Hex = 0-1: 1) using silica gel to obtain methyl 3-(4,5-dichlorothiazol-2-yl)-3-[(3,3-dimethyl-2-oxo-indolin-6-yl)amino]propanoate (180 mg, 0.434 mmol, 24.5% yield) as a yellow solid. Mass(m/z): 414.2[M+H]⁺

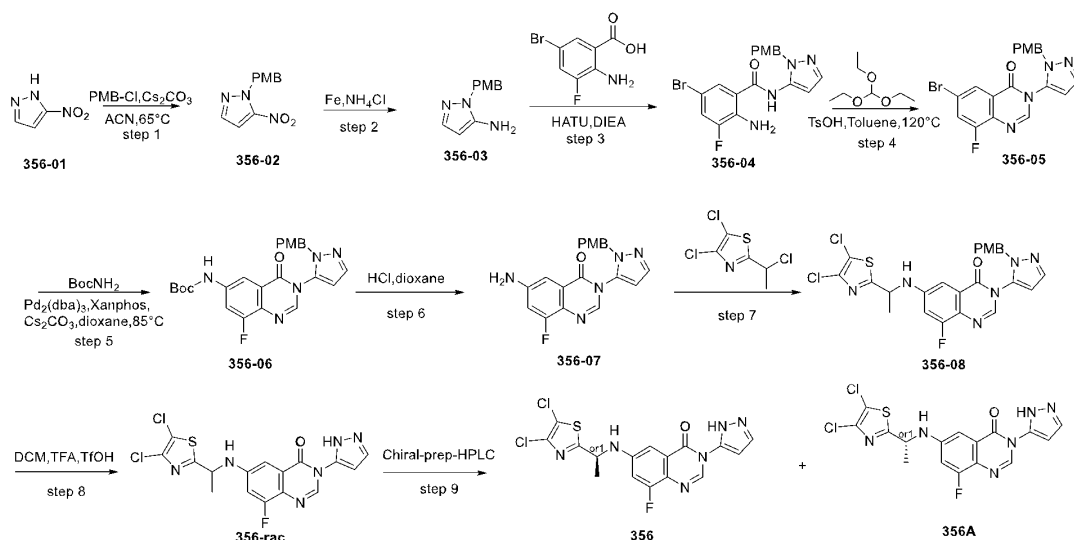
Step 3: To a solution of **292-2** (1.00 eq, 60 mg, 0.145 mmol) in Methanol (15mL) was added NaBH₄ (10.0 eq, 55 mg, 1.45 mmol). The mixture was stirred for 5 hrs at r.t. and then 20 mL of water was added. The resulting solution was extracted with EA and concentrated in vacuo. The residue was subjected to flash column chromatography (EA: Hex = 0-1) using silica gel to obtain the final product **292** (25 mg, 0.065 mmol, 44.5% yield) as a white solid. Mass (m/z): 386.2[M+H]⁺ ¹H NMR (400 MHz, Methanol-*d*₄) δ 10.87 (s, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 5.6 Hz, 1H), 7.03 – 6.93 (m, 2H), 5.56 – 5.45 (m, 2H), 4.37 (s, 2H), 2.90 – 2.71 (m, 2H), 1.97 (s, 6H).

Compounds 293 and 294 was synthesized using a similar method to that used in **292**.

Example (Compound) No. Method	Structure and Name	Appearance and Yield	¹ H NMR Data	MS (m/z) [M+H] ⁺
Example 293 Method 14 Mixture of Stereoisomers	 7-((1-(4,5-dichlorothiazol-2-yl)-3,5-dihydroxypentyl)amino)-4-methylphthalazin-1(2H)-one	white solid, yield: 44.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.09 (s, 1H), 7.75 – 7.67 (m, 1H), 7.55 – 7.46 (m, 1H), 7.31 – 7.19 (m, 2H), 5.14 – 4.94 (m, 1H), 4.74 (s, 1H), 4.37 (s, 1H), 3.80 (s, 1H), 3.58 – 3.46 (m, 2H), 2.40 (s, 3H), 2.09 – 1.92 (m, 2H), 1.65 – 1.46 (m, 3H).	429.3
Example 294 Method 14 Mixture of Stereoisomers	 6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-8-fluoro-3-(1H-pyrazol-5-yl)quinazolin-4(3H)-one	white solid, yield: 26.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.09 (s, 1H), 7.70 (d, <i>J</i> = 8.7 Hz, 1H), 7.50 (d, <i>J</i> = 6.6 Hz, 1H), 7.36 – 7.16 (m, 2H), 5.05 – 4.92 (m, 1H), 4.75 (t, <i>J</i> = 5.0 Hz, 1H), 3.62 – 3.55 (m, 2H), 2.40 (s, 3H), 2.20 – 1.96 (m, 2H).	385.3

Preparation of 6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-8-fluoro-3-(1H-pyrazol-5-yl)quinazolin-4(3H)-one (356-rac), rel-(S)-6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-8-fluoro-3-(1H-pyrazol-5-yl)quinazolin-4(3H)-one (356) and rel-(R)-6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-8-fluoro-3-(1H-pyrazol-5-yl)quinazolin-4(3H)-one

5 **(356A) Method 15**



Step 1: To a solution of **356-01** (20.0 g, 0.1769 mol) in ACN (200 mL) under nitrogen was added Cesium carbonate (172.9 g, 0.53 mol) and p-Anisyl chloride (33.12 g, 0.21 mol) at 0°C. The reaction mixture was stirred at 60°C for 16 hrs under nitrogen. The mixture was poured into water (100 mL) and extracted with EA (100 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, and concentrated in vacuum to give crude product **356-02** (15.0 g, 36.4%) as an off-white solid. MS (m/z): 234.1 [M+H]⁺.

Step 2: To a solution of **356-02** (12.0 g, 0.0515 mol) in THF (120 mL) and aqueous NH₄Cl solution (96 mL) was added Fe (17.26 g, 0.3090 mol) at 25°C. The mixture was stirred at 60°C for 4 hrs. The reaction mixture was poured into water (100 mL) and extracted with EA (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄ and concentrated in vacuum to give **356-03** (8.9 g, 85.1%) as a yellow solid. MS (m/z): 204.1 [M+H]⁺.

Step 3: To a solution of **356-03** (4.4 g, 0.02 mol) and 2-amino-5-bromo-3-fluorobenzoic acid (6.07 g, 0.026 mol) in DMF (40 mL) under nitrogen was added HATU (9.86 g, 0.0259 mol) and DIEA (8.37 g, 0.0648 mol) at 0°C. The reaction mixture was stirred at 25°C for 3 hrs under nitrogen. The reaction mixture was poured into water (100 mL) and extracted with EA (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuum to give the crude product **356-04** (20.0 g, 50%) as a yellow solid. MS (m/z): 419.0 [M+H]⁺.

Step 4: To a solution of **356-04** (10.0 g, 0.0239 mol) in toluene (100 mL) was added Triethyl orthoformate (35.4 g, 0.2390 mol) and TsOH (4.11 g, 0.0239 mol) at 20°C. The reaction

mixture was stirred at 120°C for 16 hrs. The reaction mixture was poured into water (50 mL) and extracted with EA (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuum to give crude product. The crude product was purified by silica gel (PE/EA=20/1-5/1) to give **356-05** (2.9 g, 28.32%) as a brown solid. MS (m/z): 429.0 [M+H]⁺.

Step 5: To a solution of **356-04** (2.9 g, 0.0068 mol), Boc-NH₂ (0.96 g, 0.0081 mol) and Cesium carbonate (6.65 g, 0.0204 mol) in 1,4-dioxane (30 mL) under nitrogen was added Xantphos (0.39 g, 0.0007 mol) and Pd₂(dba)₃ (0.31 g) at 20°C. The reaction mixture was stirred at 85°C for 8 hrs under nitrogen. The reaction mixture was poured into water (50 mL x 3) and extracted with EA (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuum to give crude product. The crude product was purified by silica gel (PE/EA=20/1-3/1) to give **356-06** (1.4 g, 44.5%) as a yellow solid. MS (m/z): 466.2 [M+H]⁺.

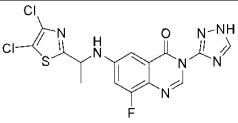
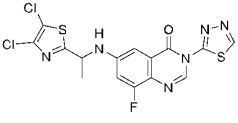
Step 6: A solution of **356-06** (1.3 g, 0.0028 mol) in DCM (10 mL) and 4 N HCl/Dioxane (5 mL) was stirred at 25°C for 3 hrs. The reaction solution was concentrated and dried in vacuum to afford the crude **356-07** (1.0 g, 98.0%) as a yellow solid. MS (m/z): 366.1 [M+H]⁺.

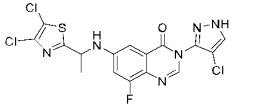
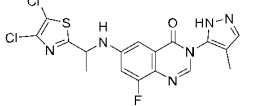
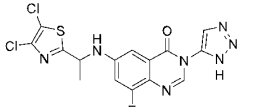
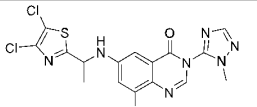
Step 7: To a solution of **356-07** (300.0 mg, 0.8211 mmol) in DMF/H₂O=1/1 (3 mL) was added 4,5-dichloro-2-(1-chloroethyl)-1,3-thiazole (355.6 mg, 1.6422 mmol), Calcium carbonate (410.9 mg, 4.1055 mmol) and potassium iodide (68.2 mg, 0.4105 mmol) at 20°C. The reaction mixture was stirred at 100°C for 16 hrs. The mixture was poured into water (20 mL) and extracted with EA (20 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄ and concentrated in vacuum to give crude product **356-08** (150 mg, 33.5%) as a yellow solid. MS (m/z): 545.1 [M+H]⁺.

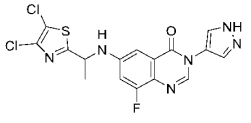
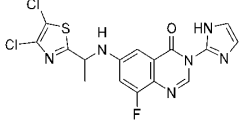
Step 8: A solution of **356-08** (150.0 mg, 0.2750 mmol) in DCM:TFA:TfOH = 3:1:0.5 (4.5 mL) was stirred at 30°C for 16 hrs. The mixture was poured into water (20 mL) and extracted with EA (20 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, and concentrated in vacuum to give crude product. The crude was purified by Prep-HPLC to give product **356-rac** (47 mg, 40.2%) as a yellow solid. MS (m/z): 425.0 [M+H]⁺.

The **356-rac** (40 mg) was purified by prep-Chiral-HPLC (Prep- Chiral HPLC conditions: Chromatographic columns: IG; Mobile Phase: Hex (0.1%TFA)-EtOH; Gradient: HEX75(0.1%TFA): EtOH25-30min-500VL) to give **356** (13.20 mg, 33.0 % yield,

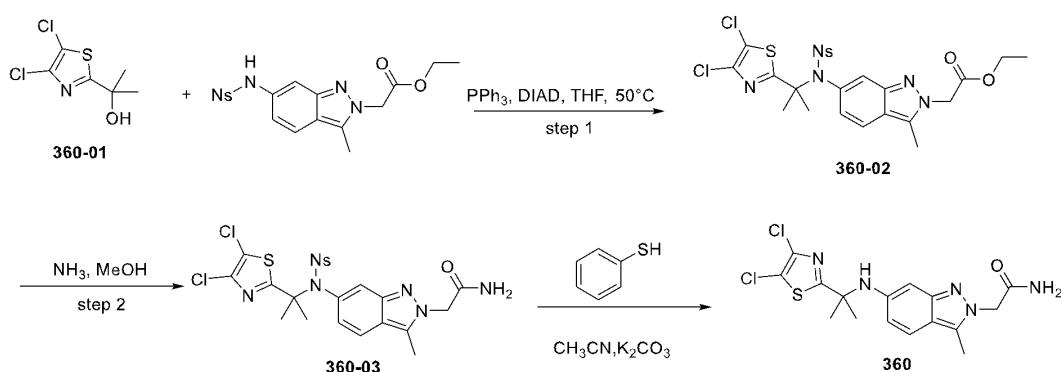
- RT= 16.628 min, single unknown stereoisomer) and **356A** (10.02 mg, 25.05 % yield, RT=23.211 min, single unknown stereoisomer) as off-white solid. **356-rac**: ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 13.12 (s, 1H), 8.32 (s, 1H), 7.90 (s, 1H), 7.50 – 7.26 (m, 1H), 7.26 – 7.00 (m, 2H), 6.64 (s, 1H), 4.98 (m, 1H), 1.58 (d, J = 6.1 Hz, 3H); **356**: ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 13.12 (s, 1H), 8.32 (s, 1H), 7.90 (s, 1H), 7.50 – 7.26 (m, 1H), 7.26 – 7.00 (m, 2H), 6.64 (s, 1H), 4.98 (m, 1H), 1.58 (d, J = 6.1 Hz, 3H). MS (m/z): 425.2 $[\text{M}+\text{H}]^+$.
- 356A**: ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 13.12 (s, 1H), 8.32 (s, 1H), 7.90 (s, 1H), 7.50 – 7.26 (m, 1H), 7.26 – 7.00 (m, 2H), 6.64 (s, 1H), 4.98 (m, 1H), 1.58 (d, J = 6.1 Hz, 3H). MS (m/z): 425.2 $[\text{M}+\text{H}]^+$.
- 10 Compounds **359** and **369-375** was synthesized using a similar method to that used in **356**.

Example (Compound) No. Method	Structure and Name	Appearance and Yield	^1H NMR Data	MS (m/z) $[\text{M}+\text{H}]^+$
Example 359 Method 15 Mixture of Stereoisomers	 6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-8-fluoro-3-(1H-1,2,4-triazol-3-yl)quinazolin-4(3H)-one	white solid, yield: 23.45 %	^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.63 (s, 1H), 8.14 (s, 1H), 7.42 (d, J = 6.4 Hz, 1H), 7.16 (dd, J = 12.4, 2.0 Hz, 1H), 7.07 (d, J = 2.0 Hz, 1H), 5.05 - 4.96 (m, 1H), 1.57 (d, J = 6.8 Hz, 3H).	425.9
Example 369 Method 15 Mixture of Stereoisomers	 6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-8-fluoro-3-(1,3,4-thiadiazol-2-yl)quinazolin-4(3H)-one	white solid, yield: 1.39%	^1H NMR (400 MHz, CDCl_3) δ 9.38 (s, 1H), 9.17 (s, 1H), 7.28 (d, J = 2.0 Hz, 1H), 6.93 (dd, J = 11.2, 2.8 Hz, 1H), 4.86 (m, 1H), 1.74 (d, J = 6.8 Hz, 3H).	442.8, 444.8

Example 370 Method 15 Mixture of Stereoisomers	 3-(4-chloro-1H-pyrazol-3-yl)-6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-8-fluoroquinazolin-4(3H)-one	White solid, yield: 21%	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.97 (s, 1H), 7.71 (s, 1H), 7.27 (s, 1H), 6.87 (dd, <i>J</i> = 11.4, 2.7 Hz, 1H), 4.84 (m, 1H), 1.71 (d, <i>J</i> = 6.8 Hz, 3H).	459.2
Example 371 Method 15 Mixture of Stereoisomers	 6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-8-fluoro-3-(4-methyl-1H-pyrazol-5-yl)quinazolin-4(3H)-one	White solid, yield: 11.09 %	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.92 (s, 1H), 8.02 (s, 1H), 7.70 (s, 1H), 7.35 (d, <i>J</i> = 6.7 Hz, 1H), 7.15 (dd, <i>J</i> = 12.6, 2.6 Hz, 1H), 7.09 (d, <i>J</i> = 2.6 Hz, 1H), 5.00 (p, <i>J</i> = 6.7 Hz, 1H), 1.88 (s, 3H), 1.58 (d, <i>J</i> = 6.7 Hz, 3H).	439.29
Example 372 Method 15 Mixture of Stereoisomers	 6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-8-fluoro-3-(1H-1,2,3-triazol-5-yl)quinazolin-4(3H)-one	white solid, yield: 51.2%	¹ H NMR (400 MHz, CDCl ₃) δ 8.77 (s, 1H), 8.45 (s, 1H), 7.26 (m, 2H), 6.96-6.80 (m, 1H), 4.86 (m, 1H), 1.73 (d, <i>J</i> = 6.8 Hz, 3H).	426.0, 428.1
Example 373 Method 15 Mixture of Stereoisomers	 6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-8-fluoro-3-(1-methyl-1H-1,2,4-triazol-5-yl)quinazolin-4(3H)-one	white solid., yield: 1.21%	¹ H NMR (400 MHz, CDCl ₃) δ 7.98 (s, 2H), 7.26 (m, 1H), 7.23 (d, <i>J</i> = 2.0 Hz, 1H), 6.93 – 6.87 (m, 1H), 4.91 – 4.80 (m, 1H), 3.84 (s, 3H), 1.72 (d, <i>J</i> = 6.8 Hz, 1H).	440.0, 442.0

Example 374 Method 15 Mixture of Stereoisomers	 rel-(S)-6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-8-fluoro-3-(1H-pyrazol-4-yl)quinazolin-4(3H)-one	off-white solid, yield: 20.00%	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.16 (s, 1H), 8.00 (s, 2H), 7.11 (d, <i>J</i> = 2.6 Hz, 1H), 7.05 (m, 1H), 4.85–4.83 (m, 1H), 1.66 (d, <i>J</i> = 6.4 Hz, 3H).	425.0, 427.0
Example 375 Method 15 Mixture of Stereoisomers	 6-((1-(4,5-dichlorothiazol-2-yl)ethyl)amino)-8-fluoro-3-(1H-imidazol-2-yl)quinazolin-4(3H)-one	white solid, yield: 4.09%	¹ H NMR (400 MHz, CDCl ₃) δ 11.43 (br, 1H), 9.21 (s, 1H), 7.25 – 7.24 (m, 2H), 7.05 (s, 2H), 6.89 (dd, <i>J</i> = 11.4, 2.6 Hz, 1H), 4.90 – 4.81 (m, 1H), 1.73 (d, <i>J</i> = 6.7 Hz, 3H).	425.0, 427.0

Preparation of 2-(6-((2-(4,5-dichlorothiazol-2-yl)propan-2-yl)amino)-3-methyl-2H-indazol-2-yl)acetamide (360)



Step 1: To a solution of **360-01** (200.0 mg, 0.943 mmol), ethyl 2-((3-methyl-6-((4-nitro-1-sulfonylphenyl) amino]indazol-2-yl} acetate (395.5 mg, 0.943 mmol) and PPh₃ (371.0 mg, 1.4145 mmol) in THF (5 mL) was added DIAD (286.0 mg, 1.4145 mmol) at 0 °C under N₂ atmosphere. The mixture was stirred at 50 °C for 16 hours. The mixture was poured into water (20 mL) and extracted with EA (10 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄ and concentrated to give the crude product. The crude product was purified by prep-TLC (PE/EA=1/1) to give the product **360-02** (120.0 mg,

20.78%) as a yellow solid. MS (m/z): 612.1, 614.1 [M+H]⁺.

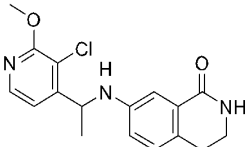
Step 2: A mixture of **360-02** (100.0 mg, 0.163 mmol) and NH₃ in MeOH (2 mL, 7 mol/L) was stirred at 25 °C for 4 hours. The mixture was concentrated to give a crude product. The crude product was purified by prep-HPLC to give the product **360-03** (11.0 mg, 11.55%) as a white

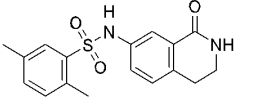
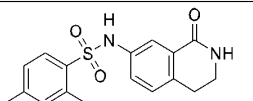
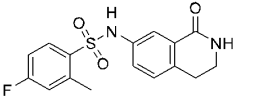
5 solid. MS (m/z): 583.1, 585.1 [M+H]⁺.

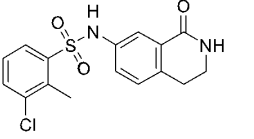
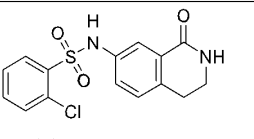
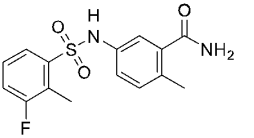
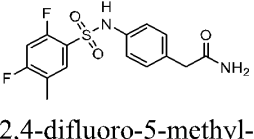
Step 3: To a solution of **360-03** (9 mg, 0.015 mmol) in CH₃CN (8 ml) was added benzenethiol (3.3 mg, 0.03 mmol), K₂CO₃ (8.5 mg, 0.06 mmol). The mixture was stirred at 25 °C for 2 hours, was added water (30 ml) and extracted with EtOAc (1 mL ×3). The solution was washed

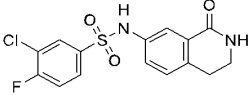
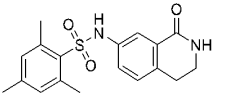
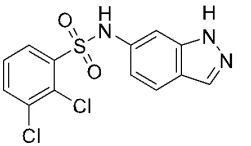
10 and dried (MgSO₄) before concentration to dryness. The crude product was purified by prep-HPLC to give the desired product as a white solid (2 mg), yield: 30.92%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.54 (m, 1H), 7.39 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.25 (m, 1H), 6.57 (dd, *J* = 9.0, 2.1 Hz, 1H), 6.38 (s, 1H), 5.82 (s, 1H), 4.83 (m, 2H), 2.42 (s, 3H), 1.65 (s, 6H). Mass (m/z): 398.31[M+H]⁺.

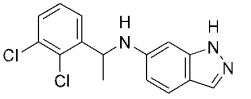
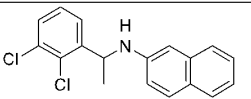
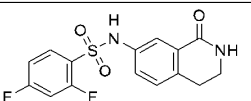
15 Compounds **1A-15A** were prepared and characterized as follows.

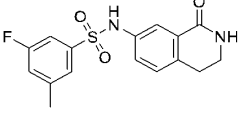
Example (Compound) No. Method	Structure and Name	Appearance and Yield	¹ H NMR Data	MS (m/z) [M+H] ⁺
Example 1A Method 2	 6-(5-(pyridazin-3-ylamino)pyridin-3-yl)benzo[d]oxazol-2(3H)-one	White solid, yield: 8.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.12 (d, <i>J</i> = 2.4 Hz, 1H), 7.87 (d, <i>J</i> = 2.4 Hz, 1H), 7.71 (s, 1H), 7.05 (s, 1H), 6.95 (d, <i>J</i> = 8.0 Hz, 1H), 6.66 (d, <i>J</i> = 8.0 Hz, 1H), 6.22 (s, 1H), 4.56 (d, <i>J</i> = 6.8 Hz, 1H), 3.89 (s, 3H), 3.25 (td, <i>J</i> = 6.4, 2.8 Hz, 2H), 2.67 (t, <i>J</i> = 6.4 Hz, 2H), 1.41 (d, <i>J</i> = 6.8 Hz, 3H).	331.11

Example 2A Method 1	 2,5-dimethyl-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 15.2%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.41 (s, 1H), 7.89 (t, <i>J</i> = 2.8 Hz, 1H), 7.70 (d, <i>J</i> = 2.0 Hz, 1H), 7.57 (d, <i>J</i> = 2.0 Hz, 1H), 7.30 (dd, <i>J</i> = 7.6, 1.6 Hz, 1H), 7.24 (d, <i>J</i> = 7.6 Hz, 1H), 7.20 – 7.11 (m, 2H), 3.28 (td, <i>J</i> = 6.4, 2.8 Hz, 2H), 2.75 (t, <i>J</i> = 6.4 Hz, 2H), 2.52 (s, 3H), 2.29 (s, 3H).	330.1
Example 3A Method 1	 2,4-dimethyl-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 15.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.39 (s, 1H), 7.88 (d, <i>J</i> = 2.8 Hz, 1H), 7.74 (d, <i>J</i> = 8.0 Hz, 1H), 7.57 (d, <i>J</i> = 2.4 Hz, 1H), 7.18 – 7.12 (m, 4H), 3.29 (td, <i>J</i> = 2.8, 6.4 Hz, 2H), 2.75 (t, <i>J</i> = 6.4 Hz, 2H), 2.54 (s, 3H), 2.28 (s, 3H).	330.8
Example 4A Method 1	 4-fluoro-2-methyl-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 26.9%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.52 (s, 1H), 7.91 – 7.87 (m, 2H), 7.56 (d, <i>J</i> = 1.6 Hz, 1H), 7.27 (dd, <i>J</i> = 9.6, 2.4 Hz, 1H), 7.21 – 7.14 (m, 3H), 3.31 – 3.22 (td, <i>J</i> = 2.8, 6.4 Hz, 2H), 2.76 (t, <i>J</i> = 6.8 Hz, 2H), 2.59 (s, 3H).	335.2

Example 5A Method 1	 3-chloro-2-methyl-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 31.4%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.71 (s, 1H), 7.90 (t, <i>J</i> = 2.8 Hz, 1H), 7.87 (dd, <i>J</i> = 8.0, 1.2 Hz, 1H), 7.71 (dd, <i>J</i> = 8.0, 1.2 Hz, 1H), 7.56 (d, <i>J</i> = 1.2 Hz, 1H), 7.38 (t, <i>J</i> = 8.0 Hz, 1H), 7.16 (d, <i>J</i> = 1.6 Hz, 2H), 3.29 (td, <i>J</i> = 6.8, 2.8 Hz, 2H), 2.77 (t, <i>J</i> = 6.8 Hz, 2H), 2.64 (s, 3H).	351.1
Example 6A Method 1	 2-chloro-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 46.1%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.67 (s, 1H), 8.01 (dd, <i>J</i> = 7.2, 1.2 Hz, 1H), 7.90 (t, <i>J</i> = 2.8 Hz, 1H), 7.64 – 7.59 (m, 3H), 7.53 (ddd, <i>J</i> = 8.4, 6.4, 2.8 Hz, 1H), 7.22 (dd, <i>J</i> = 8.0, 2.4 Hz, 1H), 7.15 (d, <i>J</i> = 8.4 Hz, 1H), 3.29 (td, <i>J</i> = 6.4, 2.8 Hz, 2H), 2.75 (t, <i>J</i> = 6.4 Hz, 2H).	337.1
Example 7A Method 1	 5-((3-fluoro-2-methylphenyl)sulfonyl)-2-methylbenzamide	White solid, yield: 35.4%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.52 (br s, 1H), 7.71 (d, <i>J</i> = 7.2 Hz, 1H), 7.63 (s, 1H), 7.45 – 7.42 (m, 2H), 7.34 (s, 1H), 7.06–6.99 (m, 3H), 2.48 (d, <i>J</i> = 4.0 Hz, 3H), 2.20 (s, 3H).	323.0
Example 8A Method 1	 2,4-difluoro-5-methyl-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	Light yellow solid, yield: 30.9%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.47 (br s, 1H), 7.77 (t, <i>J</i> = 8.2 Hz, 1H), 7.42 (d, <i>J</i> = 10.0 Hz, 1H), 7.37 (br s, 1H), 7.11 (d, <i>J</i> = 8.6 Hz, 2H), 7.02 (d, <i>J</i> = 8.6 Hz, 2H), 6.80 (br s, 1H), 3.25 (s, 2H), 2.22 (s, 3H).	341.3

Example 9A Method 1	 3-chloro-4-fluoro-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 13.3%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.47 (s, 1H), 7.96 (s, 1H), 7.92 (dd, <i>J</i> = 6.8, 2.4 Hz, 1H), 7.78 – 7.70 (m, 1H), 7.63 (t, <i>J</i> = 8.8 Hz, 1H), 7.58 (s, 1H), 7.22 (d, <i>J</i> = 1.6 Hz, 2H), 3.34 – 3.26 (m, 2H), 2.80 (t, <i>J</i> = 6.6 Hz, 2H).	354.7
Example 10A Method 1	 2,4,6-trimethyl-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 30.0%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.27 (s, 1H), 7.89 (d, <i>J</i> = 2.8 Hz, 1H), 7.54 (d, <i>J</i> = 2.4 Hz, 1H), 7.15 (d, <i>J</i> = 8.2 Hz, 1H), 7.08 (dd, <i>J</i> = 8.1, 2.4 Hz, 1H), 6.99 (s, 2H), 3.31 – 3.23 (m, 2H), 2.75 (t, <i>J</i> = 6.6 Hz, 2H), 2.57 (s, 6H), 2.20 (s, 3H).	345.1
Example 11A Method 1	 2,3-dichloro-N-(1H-indazol-6-yl)benzenesulfonamide (2H)-one	White solid, yield: 25.4%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.87 (s, 1H), 10.90 (s, 1H), 8.02 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.94 (s, 1H), 7.90 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.62 (d, <i>J</i> = 8.6 Hz, 1H), 7.52 (t, <i>J</i> = 8.0 Hz, 1H), 7.25 – 7.20 (m, 1H), 6.92 (dd, <i>J</i> = 8.6, 2.0 Hz, 1H).	342.1

Example 12A Method 2	 N-(1-(2,3-dichlorophenyl)ethyl)-1H-indazol-6-amine	White solid, yield: 9.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.25 (br s, 1H), 7.72 – 7.67 (m, 1H), 7.50 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.43 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.38 (d, <i>J</i> = 8.8 Hz, 1H), 7.29 (t, <i>J</i> = 8.0 Hz, 1H), 6.69 (d, <i>J</i> = 6.4 Hz, 1H), 6.60 (dd, <i>J</i> = 8.8, 2.0 Hz, 1H), 5.94 (s, 1H), 4.85 – 4.78 (m, 1H), 1.46 (d, <i>J</i> = 6.8 Hz, 3H).	306.1
Example 13A Method 2	 N-(1-(2,3-dichlorophenyl)ethyl)naphthalen-2-amine	White solid, yield: 3.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.60 (d, <i>J</i> = 8.8 Hz, 2H), 7.48 (td, <i>J</i> = 8.0, 1.2 Hz, 2H), 7.38 (d, <i>J</i> = 8.0 Hz, 1H), 7.28 (t, <i>J</i> = 8.0 Hz, 1H), 7.23 (t, <i>J</i> = 7.4 Hz, 1H), 7.09 (dd, <i>J</i> = 11.2, 4.0 Hz, 1H), 7.02 (dd, <i>J</i> = 8.8, 2.0 Hz, 1H), 6.78 (d, <i>J</i> = 7.2 Hz, 1H), 6.34 (d, <i>J</i> = 2.0 Hz, 1H), 4.94 (p, <i>J</i> = 6.8 Hz, 1H), 1.49 (d, <i>J</i> = 6.8 Hz, 3H).	316.2
Example 14A Method 1	 2,4-difluoro-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 45.5%	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.74 (s, 1H), 7.94 (t, <i>J</i> = 2.8 Hz, 1H), 7.87 (td, <i>J</i> = 8.6, 6.2 Hz, 1H), 7.60 (d, <i>J</i> = 2.0 Hz, 1H), 7.54 (ddd, <i>J</i> = 11.2, 9.0, 2.4 Hz, 1H), 7.31 – 7.16 (m, 3H), 3.30 (td, <i>J</i> = 6.6, 2.8 Hz, 2H), 2.79 (t, <i>J</i> = 6.6 Hz, 2H).	338.3

Example 15A Method 1	 3-fluoro-5-methyl-N-(1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzenesulfonamide	White solid, yield: 10%	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.54 (d, <i>J</i> = 2.3 Hz, 1H), 7.39 – 7.29 (m, 2H), 7.21 – 7.17 (m, 2H), 7.11 (d, <i>J</i> = 8.2 Hz, 1H), 7.06 (d, <i>J</i> = 9.5 Hz, 1H), 3.35 (t, <i>J</i> = 6.7 Hz, 2H), 2.81 (t, <i>J</i> = 6.7 Hz, 2H), 2.27 (s, 3H).	335.3
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Example II. SARM1 (50-724) Enzymatic Assay

[00239] An enzymatic assay was performed in a 384-well plate using Dulbecco's phosphate-buffered saline (PBS) as the reaction buffer. Purified SARM1 (50-724) with a final concentration of 2 nM was pre-incubated with a test compound at 1% DMSO final assay concentration for 15 min at room temperature. The reaction was initiated by adding a mixture of 200 μ M nicotinamide mononucleotide (NMN) as activator and 100 μ M NAD⁺ as substrate. After 1 h of incubation at room temperature, the reaction was terminated with 10 times volume of 70% acetonitrile, then centrifuged at 3800 rpm for 10 min. The samples were analyzed using LC-MS/MS after diluted to a proper concentration by 10 mM ammonium acetate (pH 9.75).

[00240] SARM1 inhibitory activity of Compounds 1-391 and Compounds 1A to 15A is summarized in Table 3. In Table 3, activity is provided as follows: A = IC₅₀ $\leq$ 100 nM; B = 100 nM < IC₅₀ $\leq$ 500 nM; C = 500 nM < IC₅₀ $\leq$ 1000 nM; D = IC₅₀ > 1000 nM.

Table 3

Cmpd No.	IC ₅₀	Cmpd No.	IC ₅₀	Cmpd No.	IC ₅₀
1	B	2	A	3	B
4	D	5	D	6	B
7	D	8	D	9	D
10	D	11	A	12	D
13	A	14	C	15	A
16	B	17	B	18	C
19	B	20	A	21	B
22	A	23	B	24	D
25	C	26	A	27	D

28	D	29	B	30	B
31	B	32	B	33	B
34	D	35	D	36	B
37	A	38	D	39	A
40	A	41	A	42	A
43	B	44	B	45	A
46	D	47	D	48	D
49	D	50	B	51	D
52	B	53	B	54	D
55	A	56	A	57	B
58	A	59	B	60	D
61	D	62	A	63	B
64	B	65	A	66	D
67	B	68	A	69	A
70	A	71	B	72	A
73	A	74	B	75	A
76	B	77	B	78	A
79	B	80	B	81	A
82	A	83	B	84	A
85	B	86	B	87	B
88	A	89	B	90	B
91	A	92	B	93	C
94	D	95	C	96	D
97	C	98	D	99	D
100	B	101	B	102	B
103	A	104	C	105	B
106	D	107	B	108	B
109	B	110	B	111	A
112	A	113	C	114	B
115	D	116	D	117	B
118	A	119	C	120	D
121	C	122	C	123	D
124	D	125	C	126	B

127	D	128	A	129	C
130	B	131	B	132	A
133	B	134	D	135	A
136	A	137	A	138	A
139	B	140	C	141	D
142	C	143	A	144	B
145	C	146	A	147	B
148	D	149	B	150	D
151	B	152	A	152A	C
153	A	154	B	155	B
156	A	157	B	158	D
159	C	160	C	161	D
162	D	163	D	164	D
165	D	166	D	167	D
168	D	169	D	170	D
171	B	172	D	173	D
174	B	175	D	176	D
177	D	178	D	179	B
180	B	181	B	182	D
183	B	184	B	185	A
186	B	187	A	188	A
189	A	190	B	191	A
192	A	193	A	194	A
194A	A	194B	D	195	A
196	A	197	A	198	A
199	A	200	B	201	A
201A	D	202	A	203	A
204	A	205	A	206	B
207	A	208	A	209	A
210	A	211	A	212	A
213	A	214	B	215	A
216	A	217	B	218	A
219	A	220	A	221	B

222	A	223	A	224	A
225	B	226	A	226A	D
226B	A	227	A	228	B
229	B	230	B	231	A
232	B	233	B	234	A
234A	D	235	A	236	B
237	A	237A	C	238	A
239A	A	239B	D	240	A
241	A	242	A	243	A
244	A	245	B	246	A
247	A	248	B	249	A
250	A	251	A	252	A
253	A	254	A	255	A
256	A	257	A	258	A
259	A	260	B	261	A
262	B	263	A	264	A
265	A	266	A	267	A
268	B	269	A	270	A
270A	B	271	A	272	A
273	A	274	A	275	A
276	A	277	A	278	A
279	A	280	A	281	A
282	A	283	A	284	A
285	A	286	A	287	A
288	A	289	A	290	A
291	A	292	A	293	B
294	A	295	A	296	A
297	A	298	A	299	A
300	A	301	A	302	A
302A	D	302B	D	302C	B
303	B	304A	A	304	A
304B	C	305	A	306	A
307	A	308	B	309	A

310	A	311	A	312	A
312A	A	312B	D	313	A
314	A	315	A	316	A
317	A	318	A	319	A
320	A	320A	D	321	A
322	A	323	A	323A	D
324	A	325	A	326	A
327	A	328	A	329	A
330	A	331	A	332	A
333	A	334	A	335	A
336	A	337	A	338	A
339	A	340	A	341	A
341A	A	341B	D	342	A
343	A	344	A	345	A
346	A	347	A	347A	D
348	A	349	A	350	B
351	A	352	A	353	A
354	A	355	A	355A	A
355B	D	356rac	A	356	A
356A	D	357	A	358	D
359	A	360	A	361	A
362	A	363	D	364	A
365	A	366	A	367	A
368	D	369	A	370	A
371	A	372	A	373	A
374	A	375	A	376	A
377	A	378	D	379	A
380	A	381	D	382	A
383	D	384	B	385	D
386	A	387	A	388	D
389	A	390	D	391	A
1A	D	2A	D	3A	D
4A	D	5A	A	6A	D

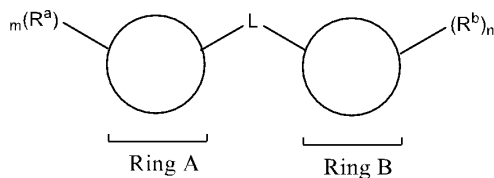
7A	D	8A	D	9A	D
10A	C	11A	B	12A	C
13A	D	14A	D	15A	D

[00241] All publications, including but not limited to disclosures and disclosure applications, cited in this specification are herein incorporated by reference as though fully set forth. If certain content of a publication cited herein contradicts or is inconsistent with the present disclosure, the present disclosure controls.

- 5 [00242] One skilled in the art will readily recognize from the disclosure and claims that various changes, modifications, and variations can be made therein without departing from the spirit and scope of the disclosure as defined in the following claims.

CLAIMS

1. A compound of the following structural Formula 1:



Formula 1

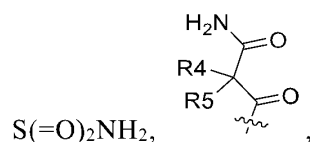
5 a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein:

Ring A is phenyl, a 5- to 10-membered heteroaryl ring, a 5 to 10-membered carbocyclic ring or a 5 to 10-membered heterocyclic ring;

10 Ring B is phenyl, a 9- to 11-membered aryl ring, a 9- to 11-membered heteroaryl ring, or a 9- to 11-membered heterocyclic ring;

R^a is selected from =O, C₃-C₆ cycloalkyl, -O(C₁-C₄ alkyl), COOH, CN, CONH₂, -C(=O)NH(C₁-C₄ alkyl), -C(=O)N(C₁-C₄ alkyl)₂, -C(=O)O(C₁-C₄ alkyl), halogen, and C₁-C₄ alkyl optionally substituted with 1 to 3 groups selected from halogen, -OH, cyclopropyl, oxetanyl, and azetidiny;

15 R^b is selected from =O, OH, halogen, CN, -C(=O)NH₂, -C(=O)NH(C₁-C₄ alkyl), -C(=O)O(C₁-C₄ alkyl), optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₃-C₆ heterocyclyl, optionally substituted C₅-C₆ heteroaryl, -O(C₁-C₄ alkyl), -C(=O)(C₁-C₄ alkyl), -C(=O)(optionally substituted C₃-C₆ cycloalkyl), -C(=O)(optionally substituted 5- to 6-membered heterocyclyl), -C(=O)(optionally substituted 5- to 6-membered heteroaryl), -C(=O)(CH₂)_pC(=O)NH₂, -NHC(=O)(C₁-C₄ alkyl), -C(=O)N(C₁-C₄ alkyl)₂, -C(=O)NH(CH₂)_pOH, -



C₁-C₄ alkyl optionally substituted with 1 to 3 groups selected from halogen, NH₂, OH, OCH₃, -C(=O)NH(C₁-C₄ alkyl), -C(=O)O(C₁-C₄ alkyl), -C(=O)N(C₁-C₄

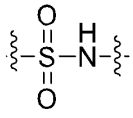
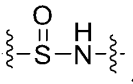
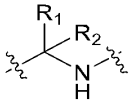
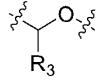
alkyl)₂, -COOH, -C(=O)NH₂, CN, C₃-C₅ cycloalkyl, phenyl, -C(=O)(C₁-C₄ alkyl), -C(=O)(C₃-C₆ cycloalkyl), -C(=O)(5- to 6-membered heterocyclyl), -C(=O)(optionally substituted 5- to 6-membered heteroaryl), C(=O)NH(CH₂)_pOH, and 5- to 6-membered heteroaryl,

5 5- to 6- membered heteroaryl optionally substituted with 1 to 2 groups selected from C₁-C₃ alkyl, =O, -NH₂, -CN, -CONH₂, halogen, and

4- to 6-membered heterocyclyl optionally substituted with 1 to 2 groups selected from =O, -OH, -NH₂, -CN, -CONH₂, halogen, and C₁-C₃ alkyl, or

two R^b attached to the same position on Ring B join to form a C₃-C₆ cycloalkyl,

10 wherein R₄ and R₅ are each independently selected from H and C₁ to C₃ alkyl or R₄ and R₅ join to form a 3- to 5-membered cycloalkyl;

L is selected from , , , and , wherein

R₁ is H, D, or C₁-C₆ alkyl, and R₂ is selected from CN, C₁-C₆ alkenyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocyclyl, 5- or 6-membered heteroaryl,

15 phenyl optionally substituted with 1 to 3 groups selected from C₁-C₄ alkyl and halogen, and

C₁-C₆ alkyl optionally substituted with 1 to 3 groups selected from halogen, OH, CN, -SO₂CH₃, -NHSO₂CH₃, -CONH₂, OCH₃, and phenyl, or

20 R₁ and R₂ join to form a 3- to 6- membered carbocyclyl or 3- to 6- membered heterocyclyl;

R₃ is C₁-C₄ alkyl optionally substituted with 1 to 3 groups selected from halogen, O(C₁-C₃ alkyl), OH, and NH₂;

m is an integer selected from 0, 1, 2, 3, and 4;

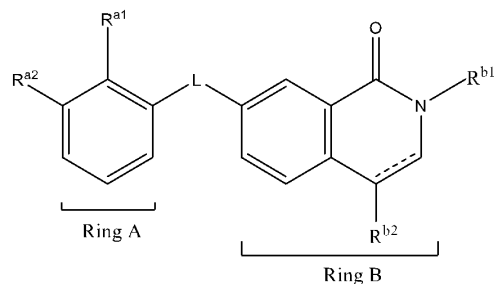
n is an integer selected from 0, 1, 2, 3, and 4, and

25 p is an integer selected from 1, 2, 3, and 4.

provided that the compound is not any of Compound 1A to Compound 121A.

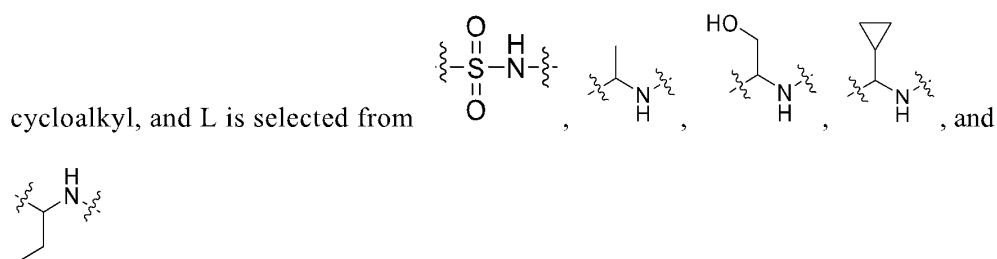
2. The compound of claim 1, wherein the compound has the following structural

Formula 14a:

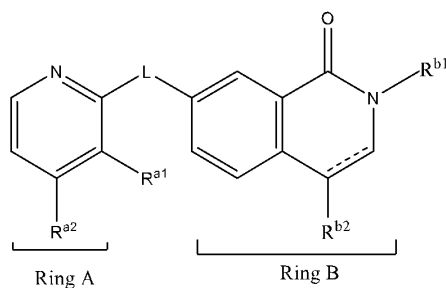


Formula 14a

- a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a
 5 pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently selected from F, Cl, Br, methyl, and OCH_3 , R^{b1} is selected from H, CH_2CN , and C_1 to C_2 alkyl, R^{b2} is selected from H, halogen, CN, OCH_3 , C_1 to C_3 alkyl, and C_3 to C_5

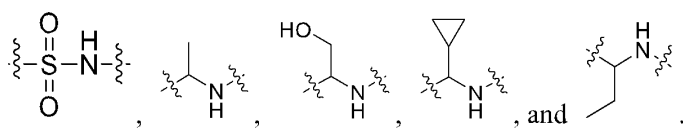


- 10 **3.** The compound of claim 1, wherein the compound has the following structural
 Formula 14b:

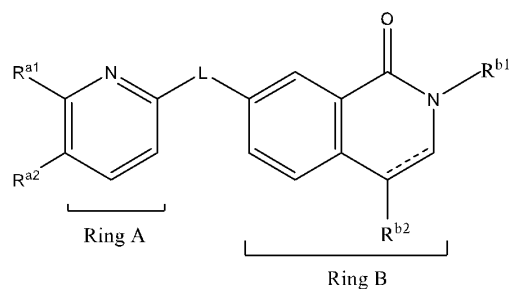


Formula 14b

- a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a
 15 pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently selected from F, Cl, Br, methyl, and OCH_3 , R^{b1} is selected from H and C_1 to C_2 alkyl, R^{b2} is selected from H, halogen, CN, OCH_3 , C_1 to C_3 alkyl, and C_3 to C_5 cycloalkyl, and L is

selected from , and .

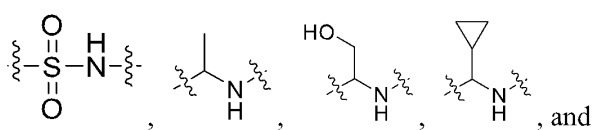
4. The compound of claim 1, wherein the compound has the following structural Formula 14c:

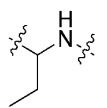


5

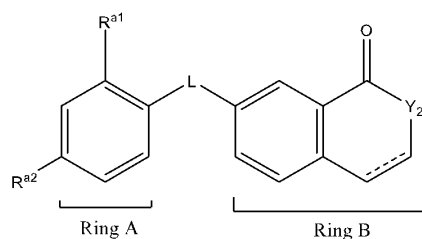
Formula 14c

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently selected from F, Cl, Br, methyl, and OCH_3 , R^{b1} is selected from H and C_1 to C_2 alkyl optionally substituted with C_3 - C_4 cycloalkyl, R^{b2} is selected from H, halogen, and C_1 to

10 C_3 alkyl, and L is selected from , and



5. The compound of claim 1, wherein the compound has the following structural Formula 14d:

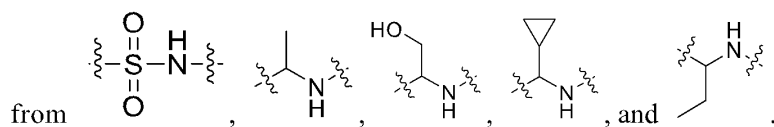


15

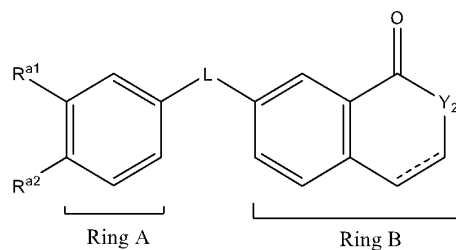
Formula 14d

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently

selected from F, Cl, Br, methyl, and OCH₃, Y₂ is selected from N and O, and L is selected



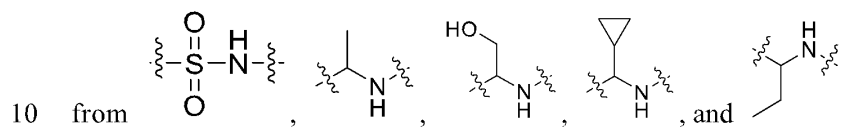
6. The compound of claim 1, wherein the compound has the following structural Formula 14e:



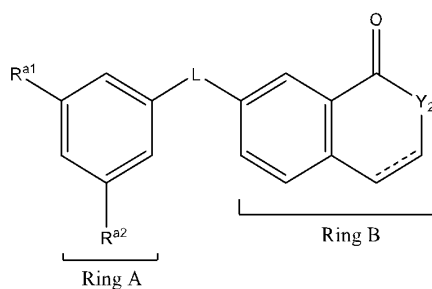
5

Formula 14e

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently selected from F, Cl, Br, methyl, and OCH₃, Y₂ is selected from N and O, and L is selected

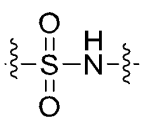
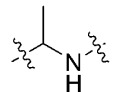
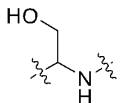
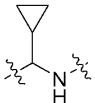
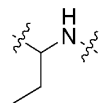


7. The compound of claim 1, wherein the compound has the following structural Formula 14f:

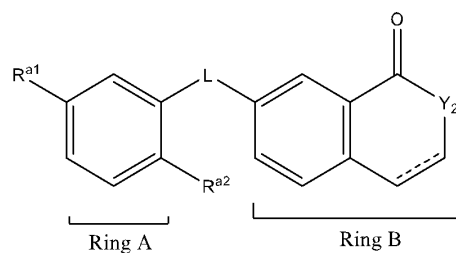


Formula 14f

15 a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently selected from F, Cl, Br, methyl, and OCH₃, Y₂ is selected from N and O, and L is selected

from , , , , and .

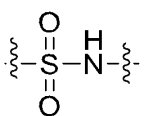
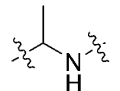
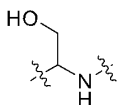
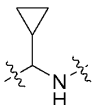
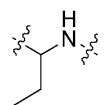
8. The compound of claim 1, wherein the compound has the following structural Formula 14g:



5

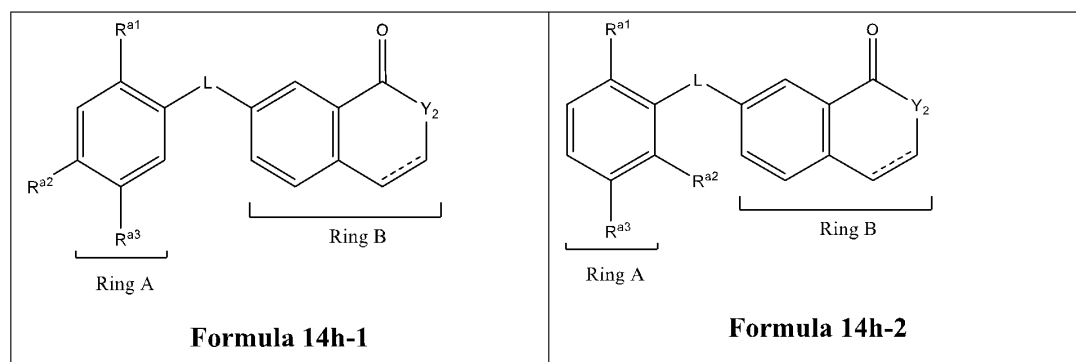
Formula 14g

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently selected from F, Cl, Br, methyl, and OCH_3 , Y_2 is selected from N and O, and L is selected

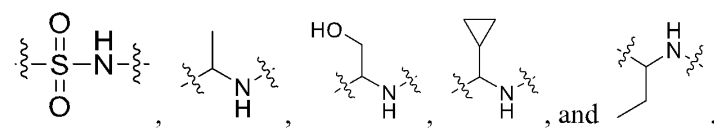
from , , , , and .

10

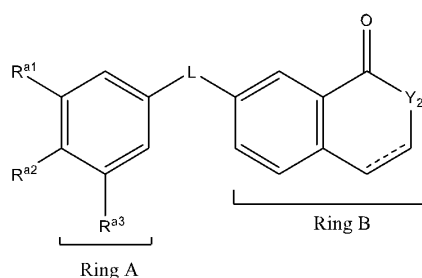
9. The compound of claim 1, wherein the compound has the following structural Formula 14h-1 or 14h-2:



a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} , R^{a2} , and R^{a3} are independently selected from F, Cl, Br, methyl, and OCH_3 , Y_2 is selected from N and O,

and L is selected from .

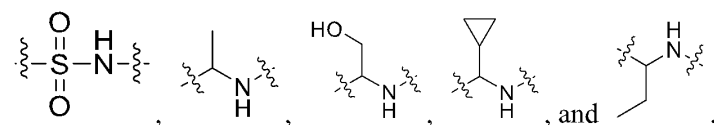
10. The compound of claim 1, wherein the compound has the following structural Formula **14i**:



5

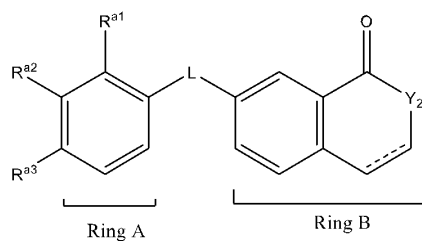
Formula 14i

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} , R^{a2} and R^{a3} are independently selected from F, Cl, Br, methyl, and OCH_3 , Y_2 is selected from N and O,

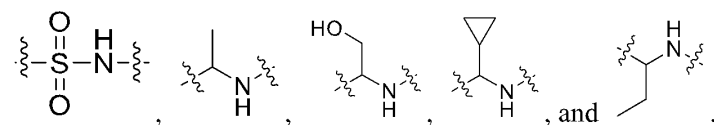
and L is selected from .

10

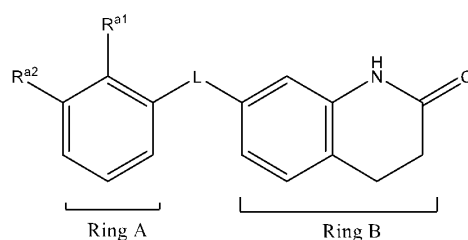
11. The compound of claim 1, wherein the compound has the following structural Formula **14j**:

**Formula 14j**

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} , R^{a2} and R^{a3} are independently selected from F, Cl, Br, methyl, and OCH_3 , Y_2 is selected from N and O,

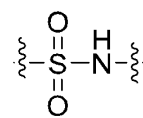
and L is selected from .

12. The compound of claim 1, wherein the compound has the following structural Formula 15a:

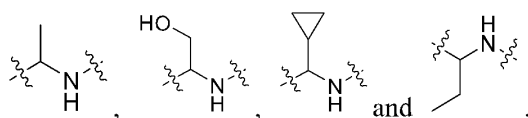


Formula 15a

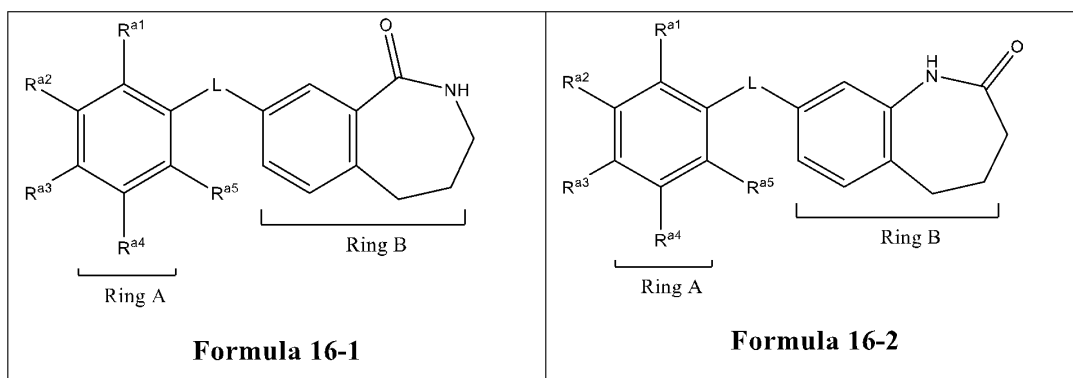
- 5 a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently



selected from F, Cl, Br, methyl, and OCH_3 , and L is selected from

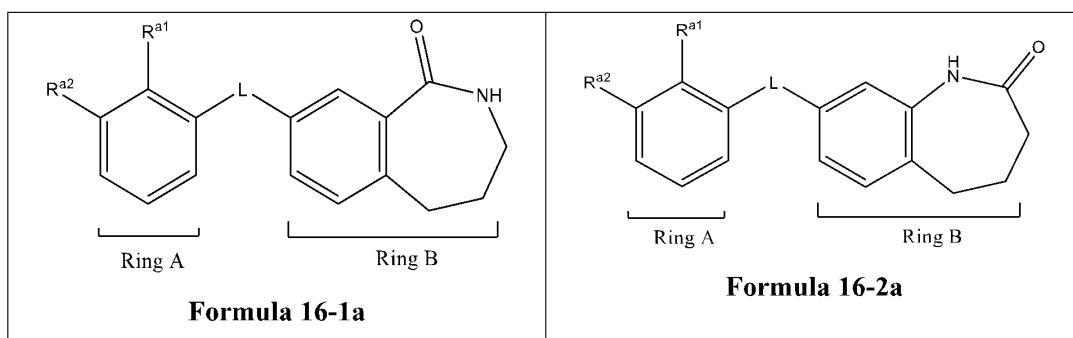


- 10 13. The compound of claim 1, wherein the compound has the following structural Formula 16-1 or 16-2:



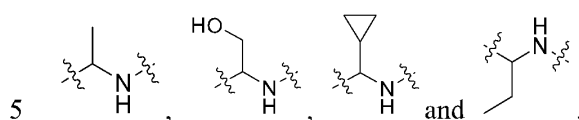
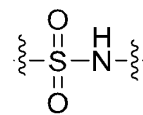
- a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein zero, one, two, or three of R^{a1} , R^{a2} , R^{a3} , R^{a4} , and R^{a5} are independently selected from F, Cl, Br, methyl, and OCH_3 , and
- 15 the rest of R^{a1} , R^{a2} , R^{a3} , R^{a4} , and R^{a5} are H.

14. The compound of any one of claims 1 and 13, wherein the compound has the following structural Formula 16-1a or 16-2a:

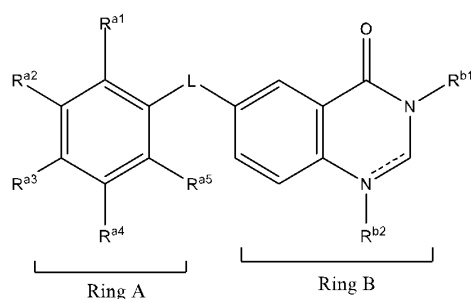


a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently

selected from F, Cl, Br, methyl, and OCH_3 , and L is selected from



15. The compound of claim 1, wherein the compound has the following structural Formula 17:

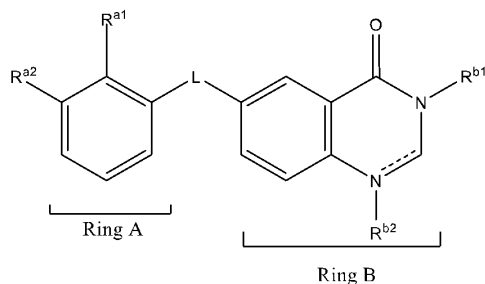


Formula 17

10 a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein zero, one, two, or three of R^{a1} , R^{a2} , R^{a3} , R^{a4} , and R^{a5} are independently selected from F, Cl, Br, methyl, and OCH_3 , and the rest of R^{a1} , R^{a2} , R^{a3} , R^{a4} , and R^{a5} are H, R^{b1} is selected from H and C_1 to C_2 alkyl, and R^{b2} is selected from H and C_1 to C_4 alkyl.

15 16. The compound of any one of claims 1 and 15, wherein the compound has the

following structural Formula 17a:

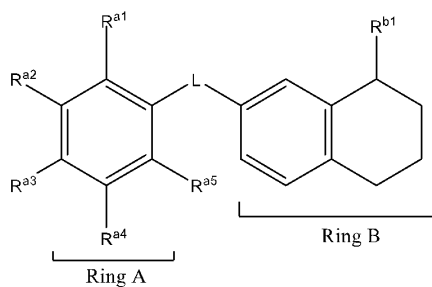


Formula 17a

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a
 5 pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently
 selected from F, Cl, Br, methyl, and OCH_3 , R^{b1} is selected from H and C_1 to C_2 alkyl, R^{b2}

is selected from H and C_1 to C_4 alkyl, and L is selected from

17. The compound of claim 1, wherein the compound has the following structural
 10 Formula 18:

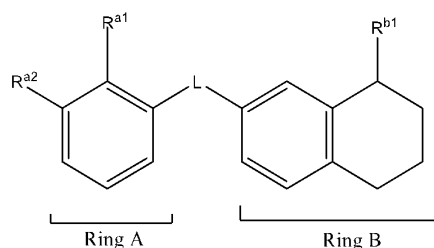


Formula 18

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a
 pharmaceutically acceptable salt of the foregoing, wherein zero, one, two, or three of R^{a1} ,
 15 R^{a2} , R^{a3} , R^{a4} , and R^{a5} are independently selected from F, Cl, Br, methyl, and OCH_3 , and
 the rest of R^{a1} , R^{a2} , R^{a3} , R^{a4} , and R^{a5} are H, R^{b1} is selected from $=O$, $-NHCOCH_3$, and
 OH.

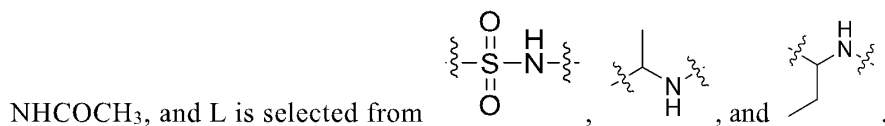
18. The compound of any one of claims 1 and 17, wherein the compound has the

following structural Formula 18a:

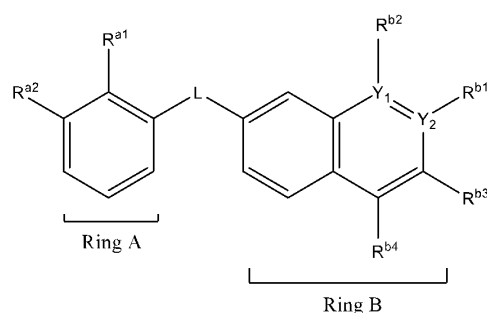


Formula 18a

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a
 5 pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently
 selected from F, Cl, Br, methyl, and OCH_3 , R^{b1} is selected from $=O$, OH, and -



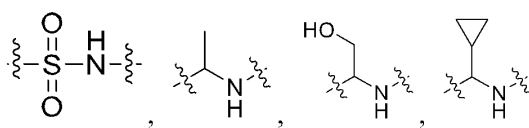
19. The compound of claim 1, wherein the compound has the following structural
 Formula 20:



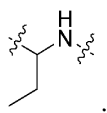
Formula 20

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a
 pharmaceutically acceptable salt of the foregoing, wherein none or one of Y_1 and Y_2 is N
 and the other is C, R^{a1} and R^{a2} are independently selected from F, Cl, Br, methyl, and
 15 OCH_3 , R^{b1} is selected from H and C_1 to C_2 alkyl provided that when Y_2 is N, R^{b1} is
 absent, R^{b2} is selected from H, CN, C_1 to C_2 alkyl, and $-C(=O)NH_2$, provided that when
 Y_1 is N, R^{b2} is absent, R^{b3} is selected from H and C_1 to C_2 alkyl, R^{b4} is selected from H

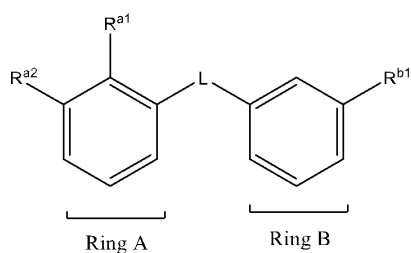
and C₁ to C₂ alkyl, and L is selected from



and



20. The compound of claim 1, wherein the compound has the following structural Formula 21a:

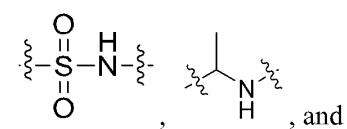


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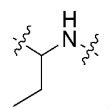
Formula 21a

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently selected from F, Cl, Br, methyl, and OCH₃, R^{b1} is selected from 5- to 6- membered heteroaryl and 5- to 6-membered heterocyclyl optionally substituted with 1 to 2 groups

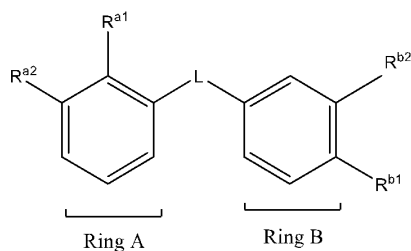
selected from =O and C₁-C₃ alkyl, and L is selected from



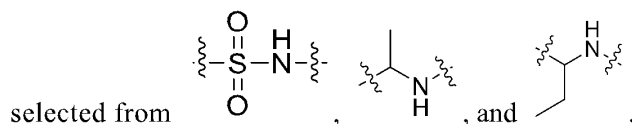
and



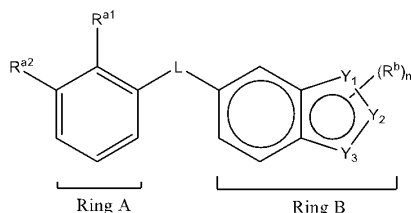
21. The compound of claim 1, wherein the compound has the following structural Formula 21b:

**Formula 21b**

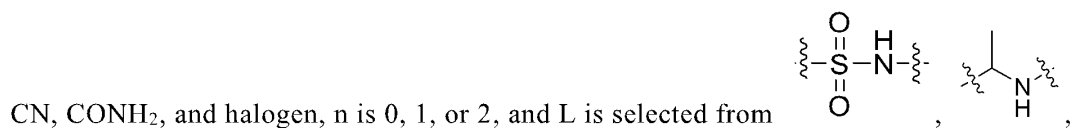
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently
 5 selected from F, Cl, Br, methyl, and OCH_3 , R^{b1} is selected from $-C(=O)NH(C_1-C_4 \text{ alkyl})$, OCH_3 , and $-C(=O)O(C_1-C_4 \text{ alkyl})$, R^{b2} is selected from H and $-C(=O)NH_2$, and L is

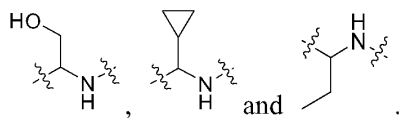


22. The compound of claim 1, wherein the compound has the following structural
 Formula 22a:

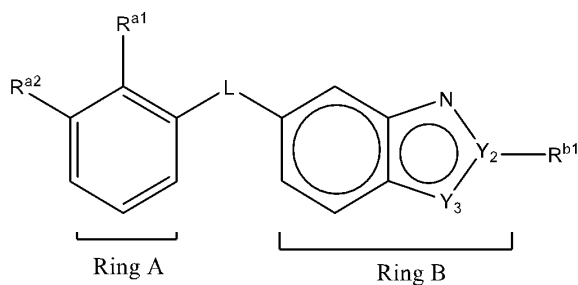
**Formula 22a**

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently
 selected from F, Cl, Br, methyl, and OCH_3 , zero, one, or two of Y_1 , Y_2 , and Y_3 are N and
 15 the rest of Y_1 , Y_2 , and Y_3 are C, R^b is selected from C_1 to C_2 alkyl, C_3 to C_5 cycloalkyl,





23. The compound of claim 1, wherein the compound has the following structural Formula 23a:

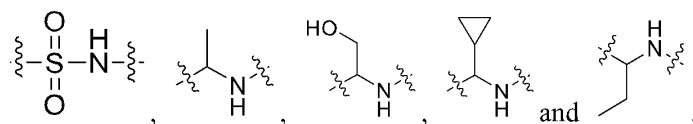


5

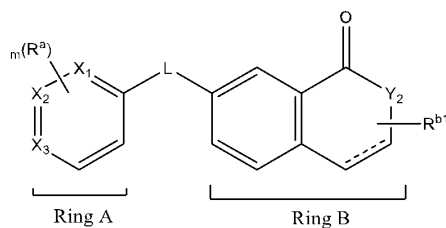
Formula 23a

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein R^{a1} and R^{a2} are independently selected from F, Cl, Br, methyl, and OCH_3 , R^{b1} is selected from H, C_1 to C_3 alkyl, halogen, C_3 - C_5 cycloalkyl, CN, and $CONH_2$ provided that when Y_2 is S or O, R^{b1} is absent, one of Y_2 and Y_3 is S or O, and the other is C, and L is selected from

10



24. The compound of claim 1, wherein the compound has the following structural Formula 24:

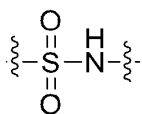


15

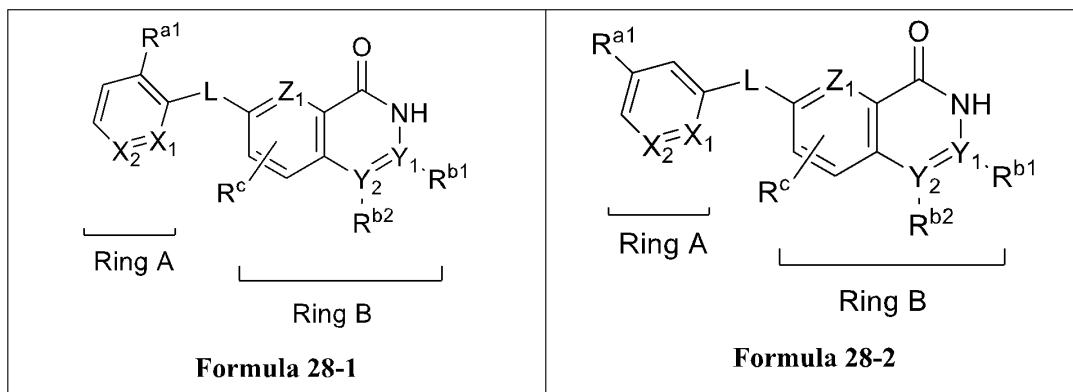
Formula 24

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein one of X_1 , X_2 , and X_3 is N and the other two of them are C, Y_2 is selected from C, N, and O, and R^{b1} is selected from C_1

to C alkyl, C₃ to C₅ cycloalkyl, O(C₁-C₃ alkyl), and halogen, and wherein L is

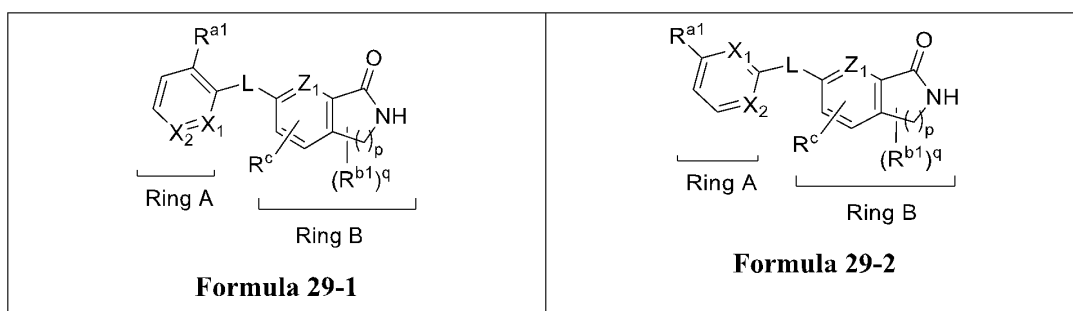


25. The compound of claim 1, wherein the compound has the following structural Formula 28-1 or 28-2:



- 5 a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X₁, X₂, Y₁, Y₂, and Z₁ are independently selected from C and N, R^{a1} is selected from F, Cl, Br, methyl, CF₃, CF₂H, CN, CONH₂, CH₂NH₂, ethyl, and cyclopropyl, R^{b1} and R^{b2} are independently selected from H, F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, cyclopropyl, and OCH₃, wherein R^{b1} and R^{b2} are absent
- 10 when connected to N in Ring B, and R^c is H, halogen, CN, or methyl.

26. The compound of claim 1, wherein the compound has the following structural Formula 29-1 or 29-2:

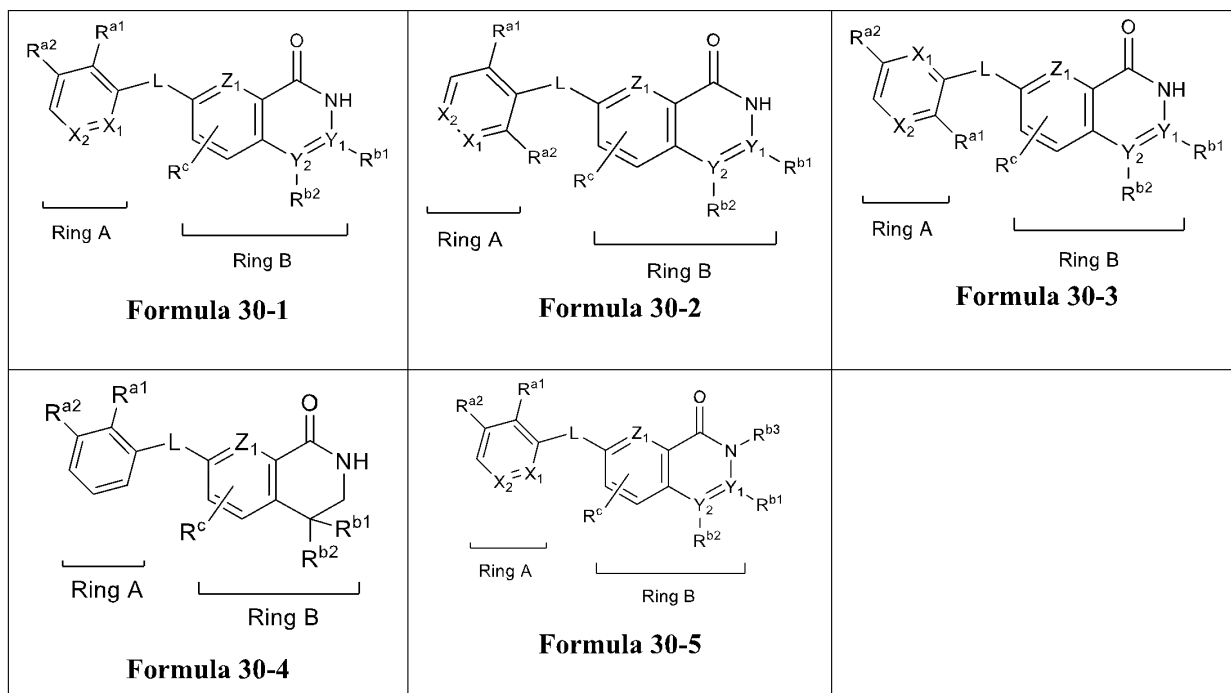


- a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X₁, X₂, and Z₁ are independently
- 15 selected from C and N, R^{a1} is selected from F, Cl, Br, methyl, CF₃, CF₂H, CN, CONH₂, CH₂NH₂, ethyl, and cyclopropyl, R^{b1} is selected from F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl,

CH₂OH, cyclopropyl, and OCH₃, wherein R^{b1} is absent or C₁ to C₄ alkyl when connected to N in Ring B, R^c is H, halogen, CN, or methyl, p is 1, 2, or 3, and q is 0, 1, or 2.

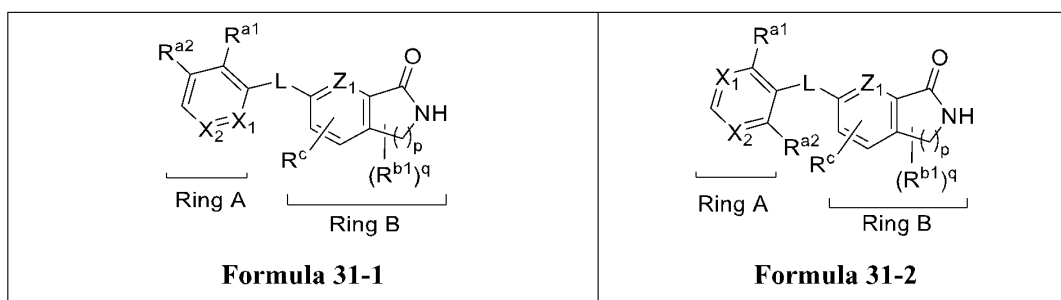
27. The compound of claim 1, wherein the compound has the following structural

Formula 30-1, 30-2, 30-3, 30-4, or 30-5:



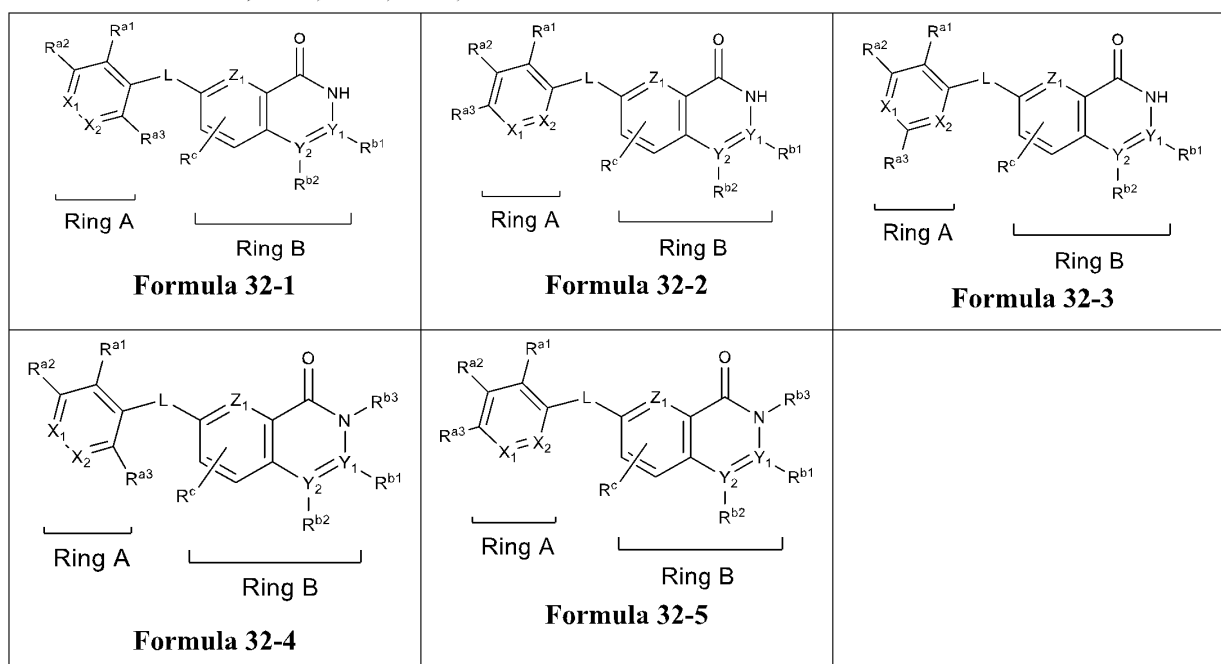
- 5 a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X₁, X₂, Y₁, Y₂, and Z₁ are independently selected from C and N, R^{a1} and R^{a2} are each independently selected from F, Cl, Br, methyl, CF₃, CF₂H, ethyl, CN, CONH₂, CH₂NH₂, and cyclopropyl, R^{b1} and R^{b2} are independently selected from H, F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, cyclopropyl, and
- 10 OCH₃, wherein R^{b1} and R^{b2} are absent when connected to N in Ring B, R^{b3} is selected from C₁ to C₄ alkyl optionally substituted with -C(=O)NH₂, 3 to 5-membered cycloalkyl optionally substituted with OH, and 5-6 membered heteroaryl optionally substituted with 1-2 groups selected from F, Cl, Br, Me, CF₃, CF₂H, CN, CONH₂, and NH₂, and R^c is H, halogen, CN, or methyl.

- 15 28. The compound of claim 1, wherein the compound has the following structural Formula 31-1 or 31-2:



a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X₁, X₂, and Z₁ are independently selected from C and N, R^{a1} and R^{a2} are each independently selected from F, Cl, Br, methyl, CF₃, CF₂H, CN, CONH₂, CH₂NH₂, ethyl, and cyclopropyl, R^{b1} is selected from F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, cyclopropyl, and OCH₃, wherein R^{b1} is absent or C₁ to C₄ alkyl when connected to N in Ring B, R^c is H, halogen, CN, or methyl, p is 1, 2, or 3, and q is 0, 1, or 2.

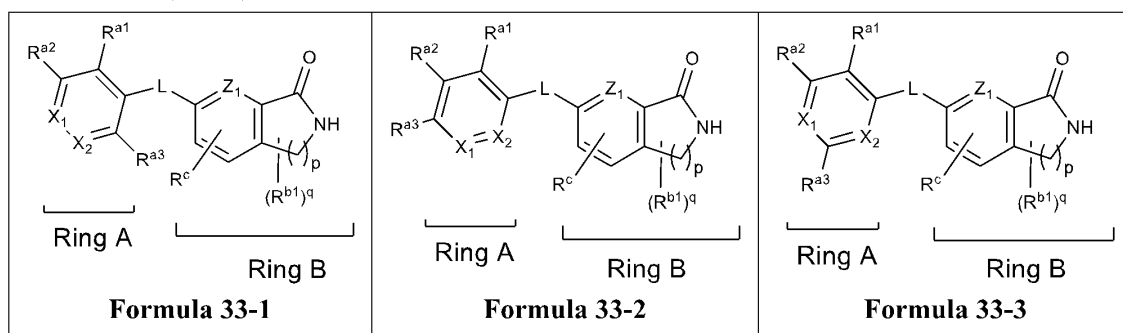
29. The compound of claim 1, wherein the compound has the following structural Formula 32-1, 32-2, 32-3, 32-4, or 32-5:



10 a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X₁, X₂, Y₁, Y₂, and Z₁ are independently selected from C and N, R^{a1}, R^{a2}, and R^{a3} are each independently selected from F, Cl, Br, methyl, CF₃, CF₂H, CN, CONH₂, CH₂NH₂, ethyl, cyclopropyl, and OCH₃, R^{b1} and R^{b2}

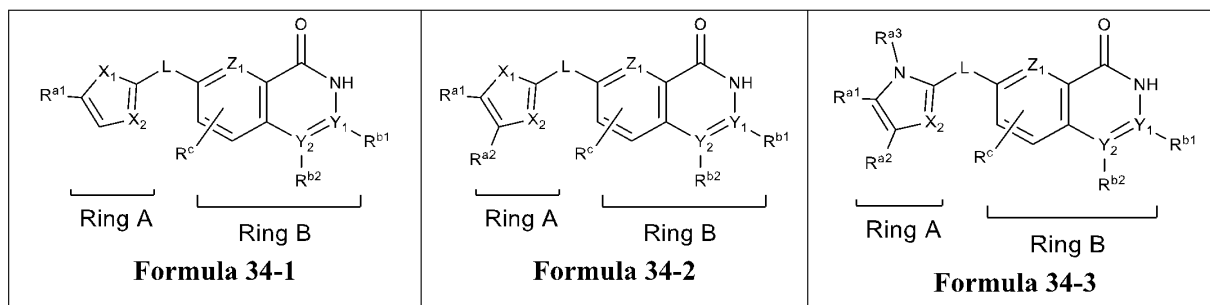
are independently selected from H, F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, cyclopropyl, and OCH₃, wherein R^{b1} and R^{b2} are absent when connected to N in Ring B, R^{b3} is selected from H, C₁ to C₄ alkyl optionally substituted with -C(=O)NH₂, 3 to 5-membered cycloalkyl optionally substituted with OH, and 5-6 membered heteroaryl optionally substituted with 1-2 groups
 5 selected from F, Cl, Br, Me, CF₃, CF₂H, CN, CONH₂, and NH₂, and R^c is H, halogen, CN, or methyl.

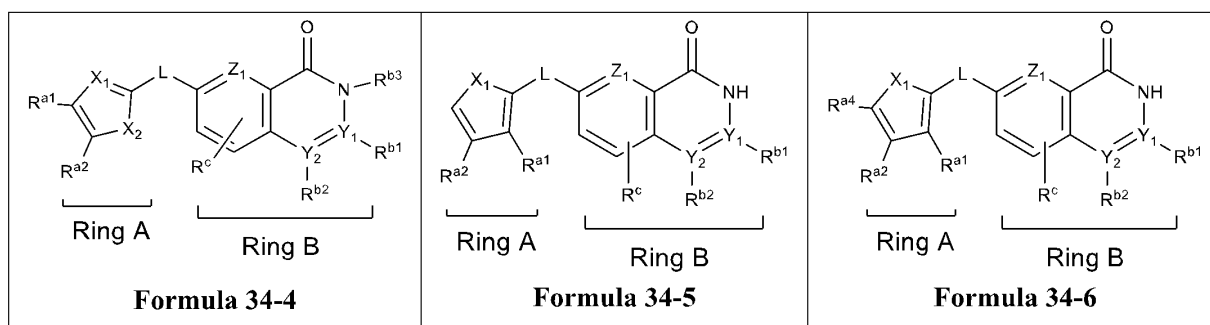
30. The compound of claim 1, wherein the compound has the following structural Formula 33-1, 33-2, or 33-3:



a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a
 10 pharmaceutically acceptable salt of the foregoing, wherein X₁, X₂, and Z₁ are independently selected from C and N, R^{a1}, R^{a2}, and R^{a3} are each independently selected from F, Cl, Br, methyl, CF₃, CF₂H, CN, CONH₂, CH₂NH₂, ethyl, cyclopropyl, and OCH₃, R^{b1} is selected from F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, cyclopropyl, and OCH₃, wherein R^{b1} is absent or C₁ to C₄ alkyl when connected to N in Ring B, and R^c is H, halogen, CN, or methyl, p is 1, 2, or 3,
 15 and q is 0, 1, or 2.

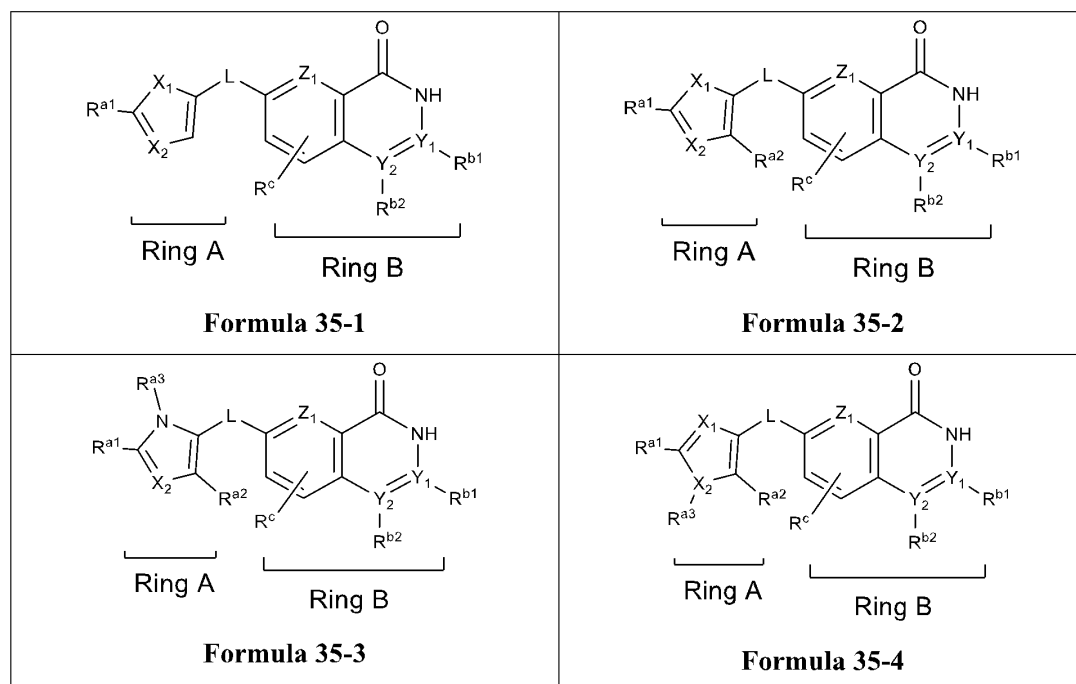
31. The compound of claim 1, wherein the compound has the following structural Formula 34-1, 34-2, 34-3, 34-4, 34-5, or 34-6:





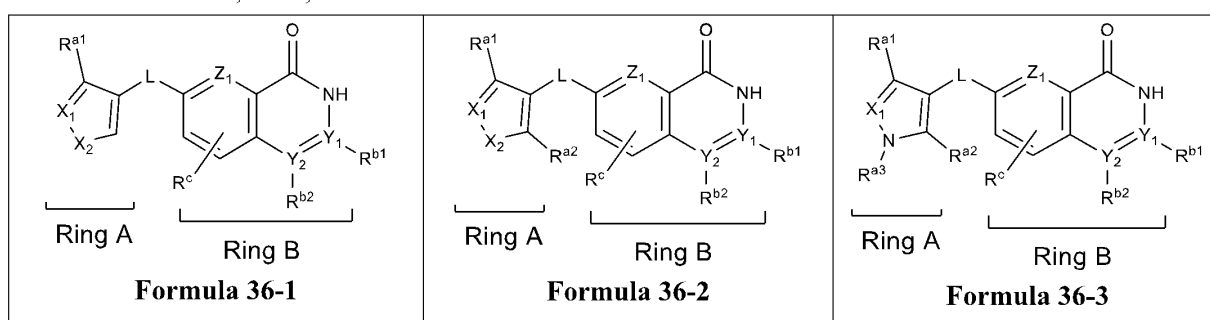
- a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X_1 and X_2 are independently selected from N, O, and S, Y_1 , Y_2 , and Z_1 are independently selected from C and N, R^{a1} and R^{a2} , and R^{a4} are each independently selected from F, Cl, Br, C_1 to C_4 alkyl, CF_3 , CF_2H , CN, $CONH_2$, CH_2NH_2 , and OCH_3 , R^{a3} is C_1 to C_4 alkyl, R^{b1} and R^{b2} are independently selected from H, F, Cl, Br, methyl, CN, CF_3 , CF_2H , ethyl, cyclopropyl, and OCH_3 , wherein R^{b1} and R^{b2} are absent when connected to N in Ring B, R^{b3} is selected from H, 5- to 6-membered heteroaryl optionally substituted with 1-2 groups selected from F, Cl, Br, Me, CF_3 , CF_2H , CN, $CONH_2$, and NH_2 , and C_1 to C_4 alkyl optionally substituted with $-C(=O)NH_2$, and R^c is H, halogen, CN, or methyl.

32. The compound of claim 1, wherein the compound has the following structural Formula 35-1, 35-2, 35-3, or 35-4:



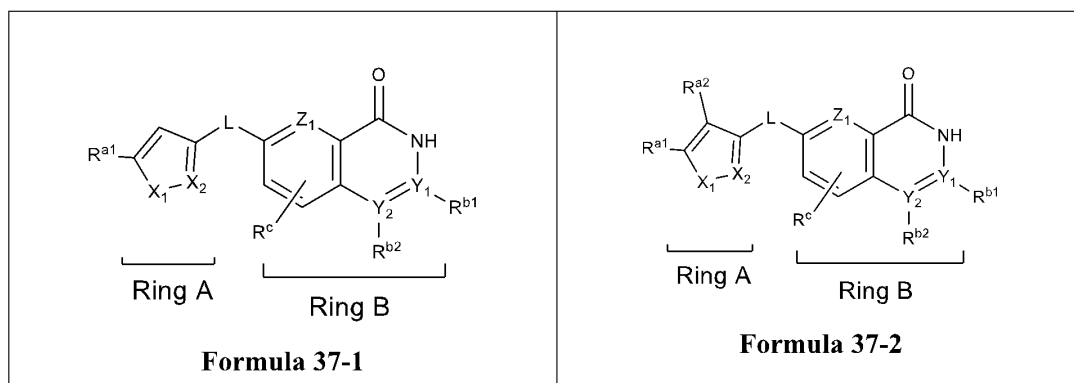
- a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X_1 and X_2 are independently selected from N, O, and S, Y_1 , Y_2 , and Z_1 are independently selected from C and N, R^{a1} and R^{a2} are each independently selected from F, Cl, Br, C_1 to C_4 alkyl, CF_3 , CF_2H , and OCH_3 , R^{a3} is C_1 to C_4 alkyl, R^{b1} and R^{b2} are independently selected from H, F, Cl, Br, methyl, CN, CF_3 , CF_2H , ethyl, cyclopropyl, and OCH_3 , wherein R^{b1} and R^{b2} are absent when connected to N in Ring B, and R^c is H, halogen, CN, or methyl.

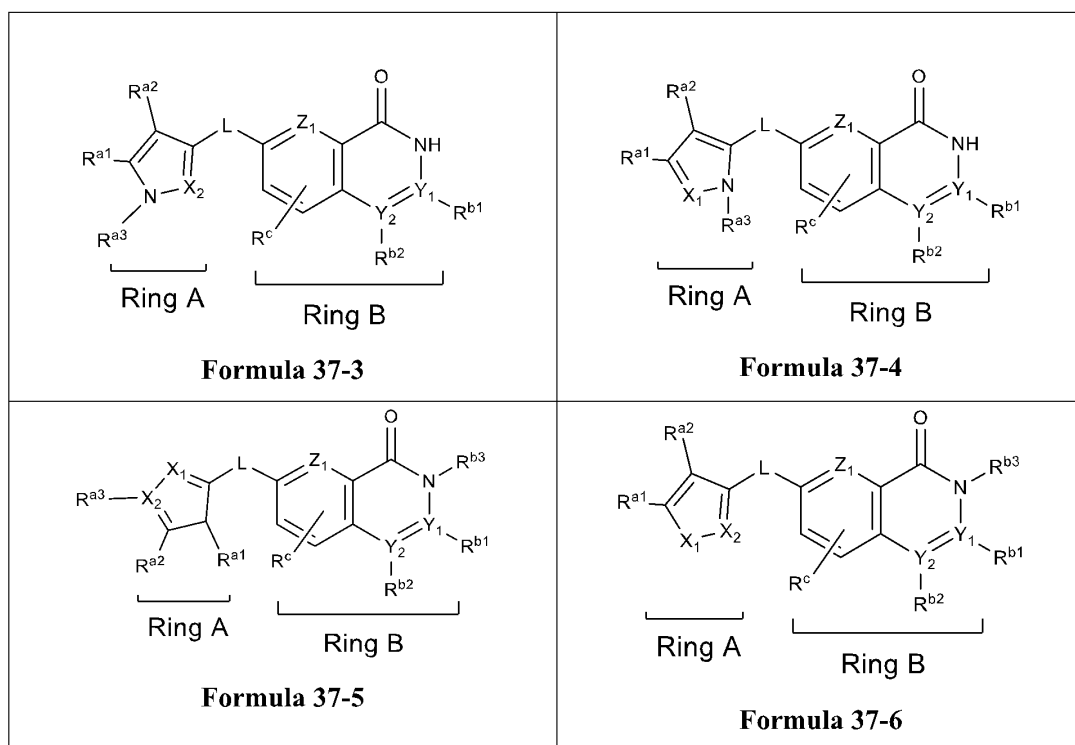
33. The compound of claim 1, wherein the compound has the following structural Formula 36-1, 36-2, or and 36-3:



- 10 a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X_1 and X_2 are independently selected from N, O, and S, Y_1 , Y_2 , and Z_1 are independently selected from C and N, R^{a1} and R^{a2} are each independently selected from F, Cl, Br, C_1 to C_4 alkyl, CF_3 , CF_2H , CN, $CONH_2$, CH_2NH_2 , and OCH_3 , R^{a3} is C_1 to C_4 alkyl, R^{b1} and R^{b2} are independently selected from H, F, Cl, Br, methyl, CN, CF_3 , CF_2H , ethyl, cyclopropyl, and OCH_3 , wherein R^{b1} and R^{b2} are absent when connected to N in Ring B, and R^c is H, halogen, CN, or methyl.

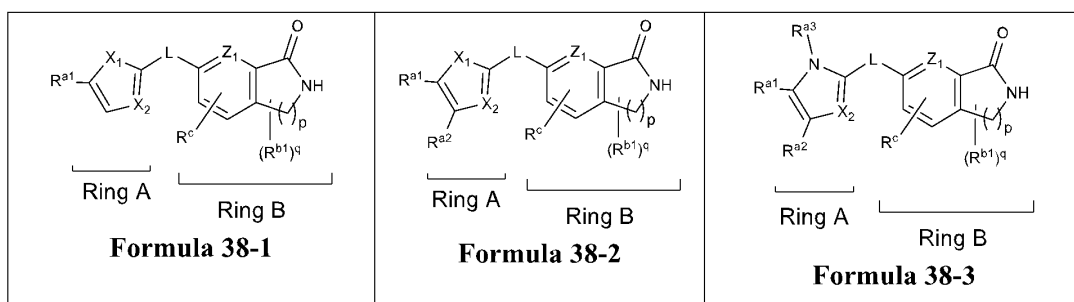
34. The compound of claim 1, wherein the compound has the following structural Formula 37-1, 37-2, 37-3, 37-4, 37-5, or 37-6:





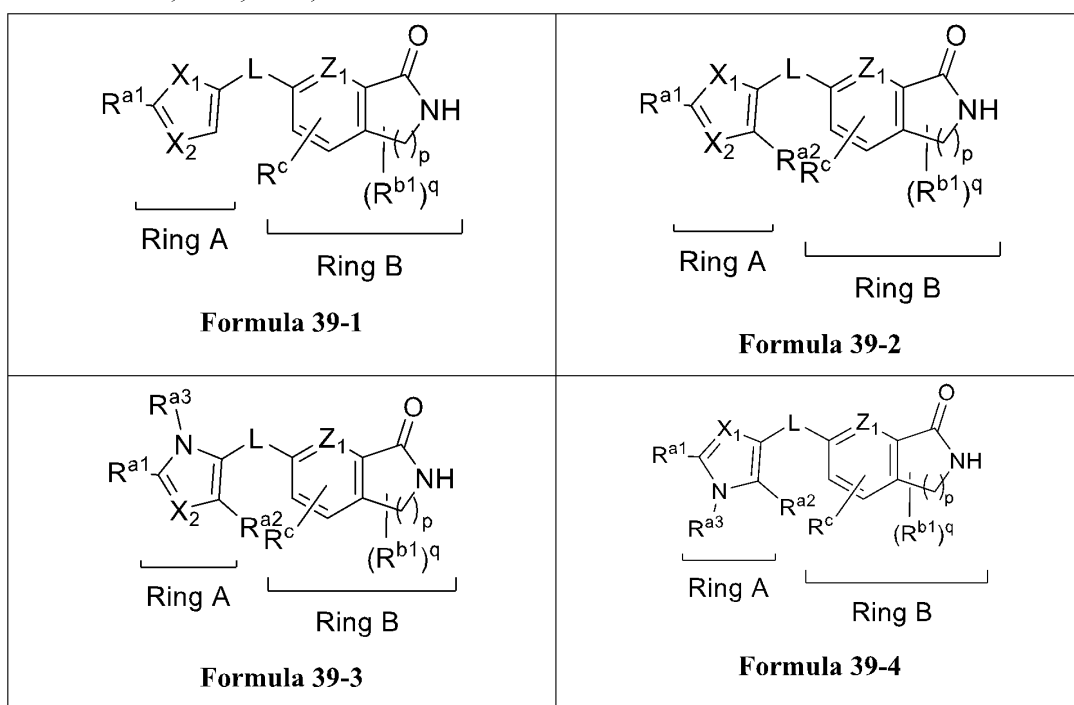
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X_1 and X_2 are independently selected from N, O, and S, Y_1 , Y_2 , and Z_1 are independently selected from C and N, R^{a1} and R^{a2} are each independently selected from F, Cl, Br, C_1 to C_4 alkyl optionally substituted with 1-3 groups of halogen, C_3 - C_4 cycloalkyl, CF_3 , CF_2H , CN, $CONH_2$, CH_2NH_2 , and OCH_3 , R^{a3} is selected from C_3 - C_4 cycloalkyl and C_1 to C_4 alkyl optionally substituted by 1 to 3 groups selected from halogen, cyclopropyl, and 4- to 5-membered heterocyclyl, R^{b1} and R^{b2} are independently selected from H, F, Cl, Br, methyl, CN, CF_3 , CF_2H , ethyl, cyclopropyl, and OCH_3 , wherein R^{b1} and R^{b2} are absent when connected to N in Ring B, R^{b3} is selected from 5- to 6-membered heteroaryl substituted with 1-2 groups selected from F, Cl, Br, Me, CF_3 , CF_2H , CN, $CONH_2$, and NH_2 , and C_1 to C_4 alkyl optionally substituted with OH or $-C(=O)NH_2$, and R^c is H, halogen, CN, or methyl.

35. The compound of claim 1, wherein the compound has the following structural Formula 38-1, 38-2, or 38-3:



a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X_1 and X_2 are independently selected from N, O, and S, Z_1 is selected from C and N, R^{a1} and R^{a2} are each independently selected from F, Cl, Br, C_1 to C_4 alkyl, CF_3 , CF_2H , CN, $CONH_2$, CH_2NH_2 , and OCH_3 , R^{a3} is C_1 to C_4 alkyl, R^{b1} is selected from F, Cl, Br, methyl, CN, CF_3 , CF_2H , ethyl, cyclopropyl, and OCH_3 , and R^c is H, halogen, CN, or methyl, p is 1, 2, or 3, and q is 0, 1, or 2.

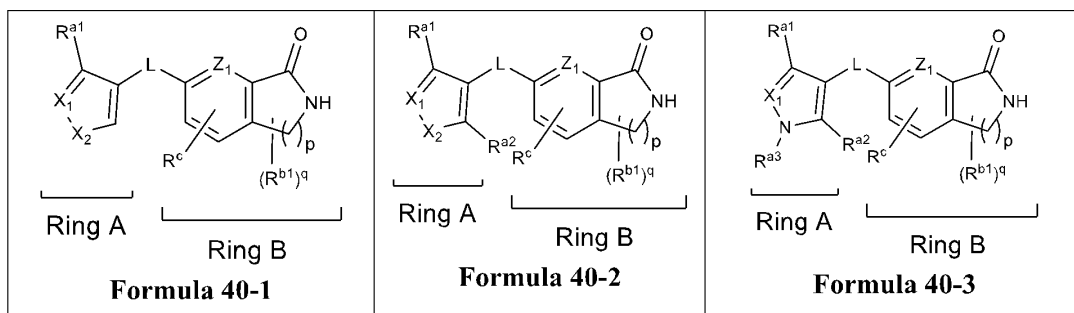
36. The compound of claim 1, wherein the compound has the following structural Formula 39-1, 39-2, 39-3, or 39-4:



a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X_1 and X_2 are independently selected from N, O, and S, Z_1 is selected from C and N, R^{a1} and R^{a2} are each independently selected from F, Cl, Br, C_1 to C_4 alkyl, CF_3 , CF_2H , CN, $CONH_2$, CH_2NH_2 , and OCH_3 , R^{a3} is C_1

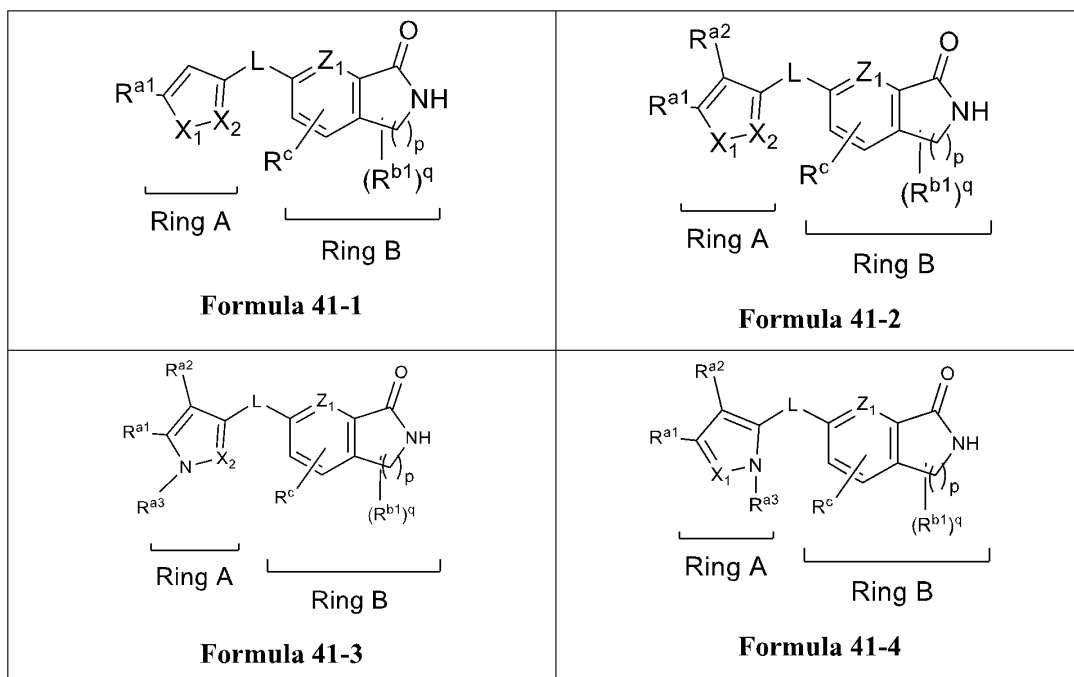
to C₄ alkyl, R^{b1} is selected from F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, cyclopropyl, and OCH₃, R^c is H, halogen, CN, or methyl, p is 1, 2, or 3, and q is 0, 1, or 2.

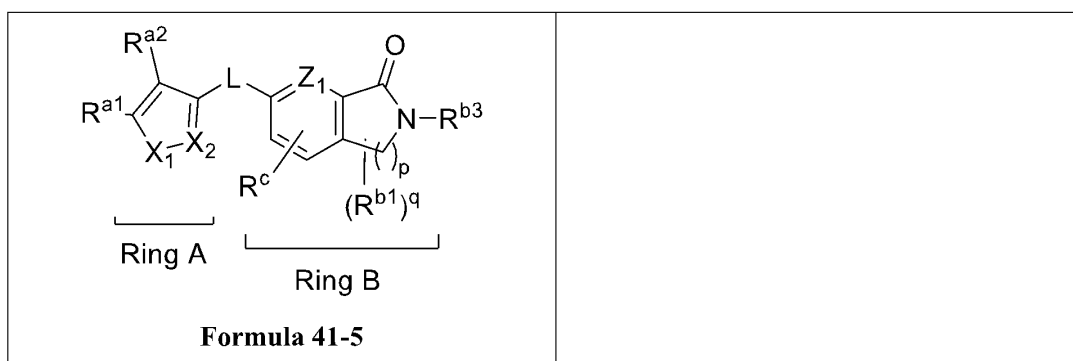
37. The compound of claim 1, wherein the compound has the following structural Formula 40-1, 40-2, or 40-3:



- 5 a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X₁ and X₂ are independently selected from N, O, and S, Z₁ is selected from C and N, R^{a1} and R^{a2} are each independently selected from F, Cl, Br, C₁ to C₄ alkyl, CF₃, CF₂H, CN, CONH₂, CH₂NH₂, and OCH₃, R^{a3} is C₁ to C₄ alkyl, R^{b1} is selected from F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, cyclopropyl, and OCH₃, R^c is H, halogen, CN or methyl, p is 1, 2, or 3, and q is 0, 1, or 2.
- 10

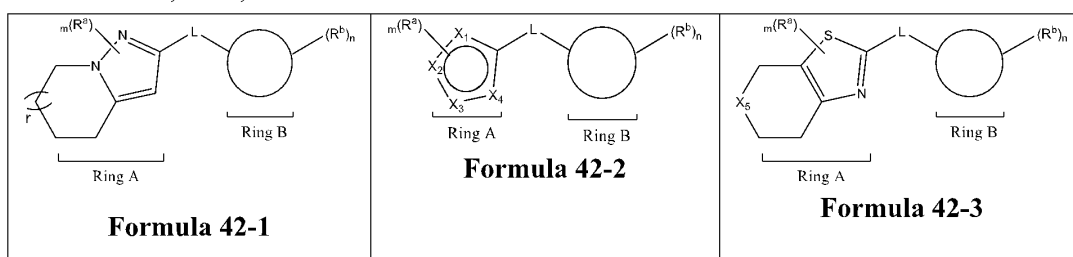
38. The compound of claim 1, wherein the compound has the following structural Formula 41-1, 41-2, 41-3, 41-4, or 41-5:





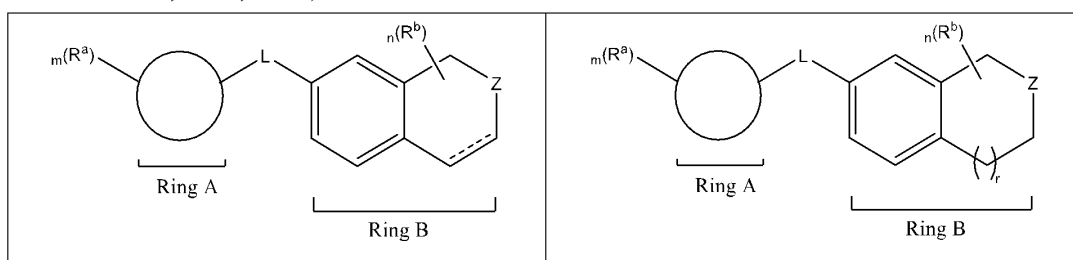
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X_1 and X_2 are independently selected from N, O, and S, Z_1 is selected from C and N, R^{a1} and R^{a2} are each independently selected from F, Cl, Br, C_1 to C_4 alkyl, CF_3 , CF_2H , CN, $CONH_2$, CH_2NH_2 , and OCH_3 , R^{a3} is C_1 to C_4 alkyl, R^{b1} is selected from F, Cl, Br, methyl, CN, CF_3 , CF_2H , ethyl, cyclopropyl, and OCH_3 , R^{b3} is selected from C_1 to C_4 alkyl optionally substituted with OH or $-C(=O)NH_2$, R^c is H, halogen, CN, or methyl, p is 1, 2, or 3, and q is 0, 1, or 2.

39. The compound of claim 1, wherein the compound has the following structural Formula 42-1, 42-2, or 42-3:



a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein X_1 , X_2 , X_3 , and X_4 are independently selected from C, N, and S, and wherein X_5 is selected from C and N, and r is an integer selected from 0, 1, and 2.

40. The compound of claim 1, wherein the compound has the following structural Formula 43-1, 43-2, 43-3, or 43-4:

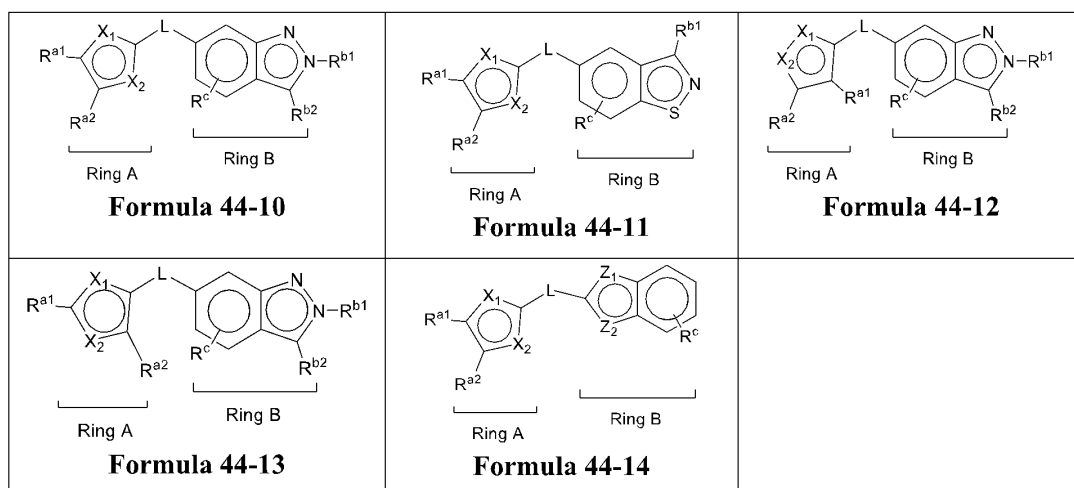


Formula 43-1	Formula 43-2
Ring A Ring B Formula 43-3	Ring A Ring B Formula 43-4

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein Z, Z₁, Z₂, and Z₃ are independently selected from C, S, and N, and r is an integer selected from 0, 1, and 2.

- 5 **41.** The compound of claim 1, wherein the compound has the following structural Formula 44-1, 44-2, 44-3, 44-4, 44-5, 44-6, 44-7, 44-8, 44-9, 44-10, 44-11, 44-12, 44-13, or 44-14:

Ring A Ring B Formula 44-1	Ring A Ring B Formula 44-2	Ring A Ring B Formula 44-3
Ring A Ring B Formula 44-4	Ring A Ring B Formula 44-5	Ring A Ring B Formula 44-6
Ring A Ring B Formula 44-7	Ring A Ring B Formula 44-8	Ring A Ring B Formula 44-9



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

X₁ is selected from C, S, O and N, X₂ is selected from C, N, S, and O, Z₁ and Z₂ are independently selected from C, N, and S,

- 5 R^{a1}, R^{a2}, and R^{a3} are each independently selected from F, Cl, Br, C₁ to C₄ alkyl, CF₃, CF₂H, CN, CONH₂, CH₂NH₂, and OCH₃,

R^{b1} is selected from H, F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, OCH₃, -C(=O)CH₂C(=O)NH₂, -C(=O)(C₁ to C₄ alkyl), -C(=O)(C₃ to C₅ cycloalkyl), -C(=O)(5- to 6-membered heteroaryl), -C(=O)(4- to 6-membered heterocyclyl optionally substituted with =O or OH), -C(=O)OH, OH,

- 10 , , -C(=O)NH₂, 3- to 5-membered cycloalkyl optionally substituted by OH, and C₁ to C₄ alkyl optionally substituted by OH or -C(=O)NH₂,

R^{b2} and R^{b3} are independently selected from H, F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, -C(=O)NH₂, and OCH₃, or R^{b2} and R^{b3} join to form a C₃ to C₅ cycloalkyl,

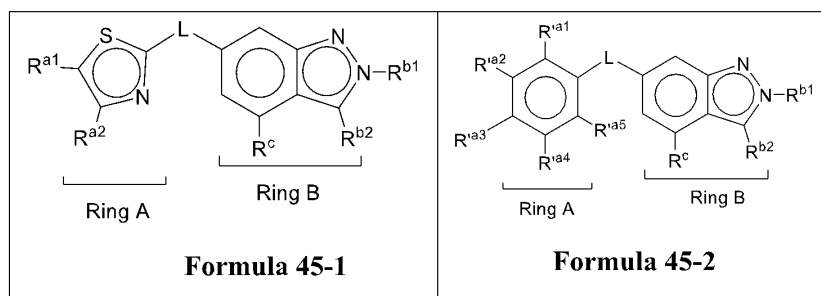
R^{b4} is =O or absent,

- 15 R^{b5} is selected from H, F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, OCH₃, -C(=O)CH₂C(=O)NH₂, -C(=O)(C₁ to C₄ alkyl), -C(=O)(C₃ to C₅ cycloalkyl), -C(=O)(5- to 6-membered heteroaryl), -C(=O)(5- to 6-membered heterocyclyl optionally substituted with =O), -C(=O)OH, OH, C₁ to C₄ alkyl optionally substituted by OH or -C(=O)NH₂, and C₃ to C₅ cycloalkyl optionally substituted with OH, and

R^c is H, halogen, CN, or methyl, and

wherein R_4 and R_5 join to form a 3 to 4-membered cycloalkyl.

42. The compound of claim 1, wherein the compound has the following structural Formula 45-1 or 45-2:



- 5 a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein

R^{a1} and R^{a2} are each independently selected from halogen and C_1 to C_2 alkyl optionally substituted with 1 to 3 groups of halogen,

R^{a1} , R^{a2} , R^{a3} , R^{a4} , and R^{a5} are each independently selected from H and halogen, wherein 2,

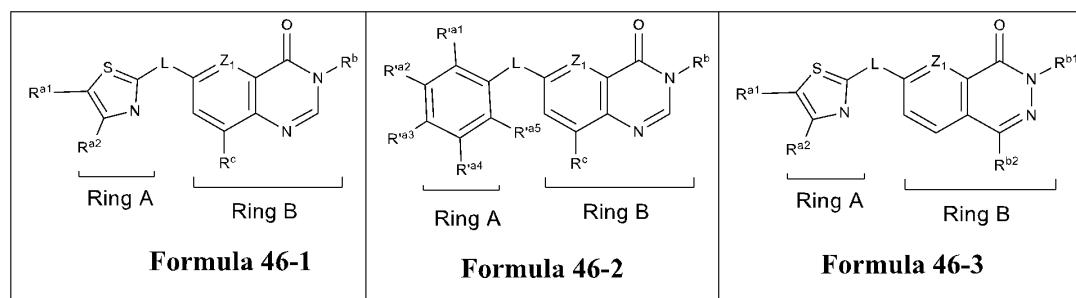
- 10 3, or 4 of R^{a1} , R^{a2} , R^{a3} , R^{a4} , and R^{a5} are halogen and the rest is H,

R^{b1} is selected from H and C_1 to C_4 alkyl optionally substituted by $-C(=O)NH_2$,

R^{b2} is selected from H and C_1 to C_4 alkyl optionally substituted by 1-3 groups of halogen, and

R^c is selected from H, halogen, and C_1 to C_2 alkyl.

- 43.** The compound of claim 1, wherein the compound has the following structural Formula 46-1, 46-2, or 46-3:



a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein

Z_1 is selected from C and N,

R^{a1} and R^{a2} are each independently selected from halogen and C_1 to C_2 alkyl optionally

substituted with 1 to 3 groups of halogen,

R^{a1} , R^{a2} , R^{a3} , R^{a4} , and R^{a5} are each independently selected from H and halogen, wherein 2, 3, or 4 of R^{a1} , R^{a2} , R^{a3} , R^{a4} , and R^{a5} are halogen and the rest is H,

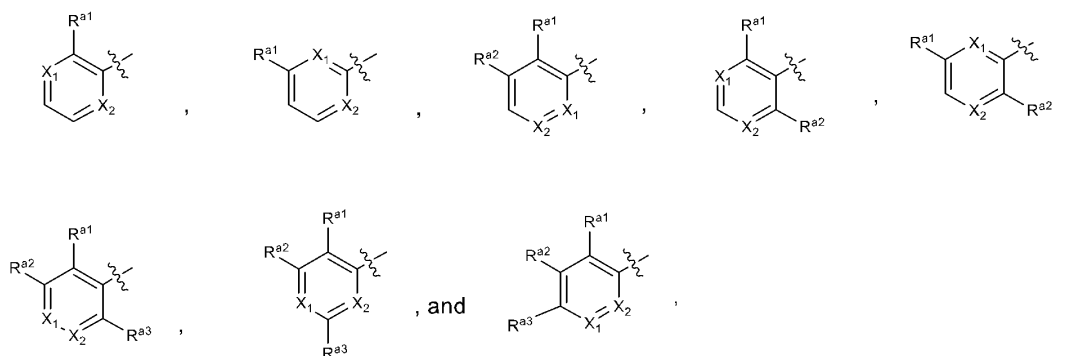
R^b is selected from H and 5- to 6-membered heteroaryl containing 2 to 3 heteroatoms selected from N and S, wherein the 5- to 6-membered heteroaryl of R^b is optionally substituted by 1 to 3 groups selected from halogen and C_1 to C_4 alkyl,

R^{b1} is selected from H and C_1 to C_4 alkyl optionally substituted by $-C(=O)NH_2$,

R^{b2} is selected from H, halogen, $-O(C_1$ to C_4 alkyl), and C_1 to C_4 alkyl optionally substituted with 1-3 groups of halogen, and

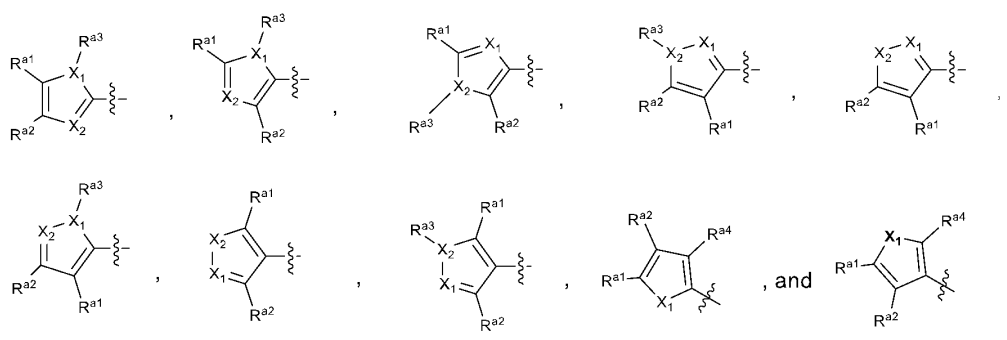
10 R^c is selected from H, halogen, and C_1 to C_2 alkyl.

44. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of claims 1 and 40, wherein Ring A substituted with m groups of R^a is selected from:



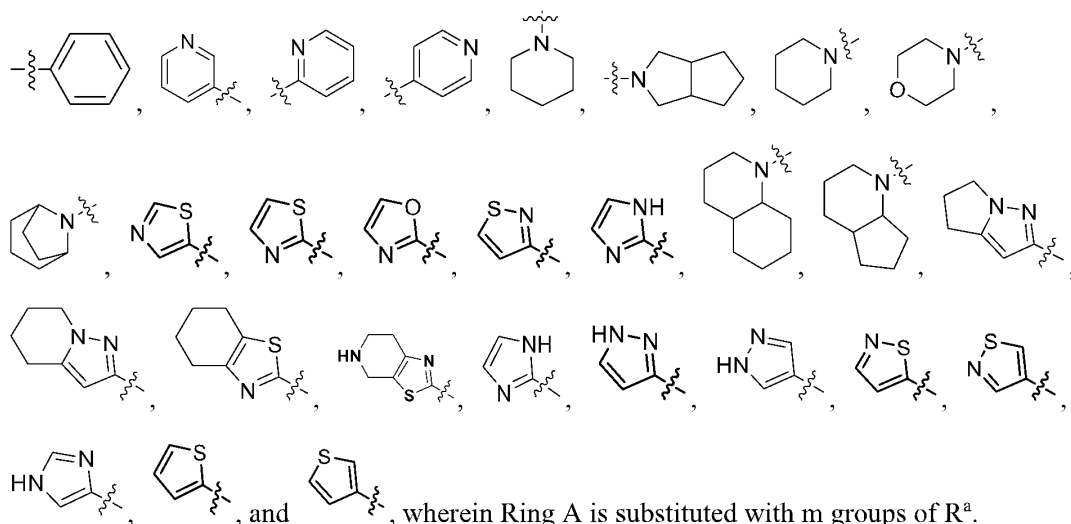
15 wherein R^{a1} , R^{a2} , and R^{a3} are independently selected from F, Cl, Br, methyl, CF_3 , CF_2H , and cyclopropyl, and X_1 and X_2 are independently selected from C and N.

45. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of claims 1 and 40, wherein Ring A substituted with m groups of R^a is selected from:



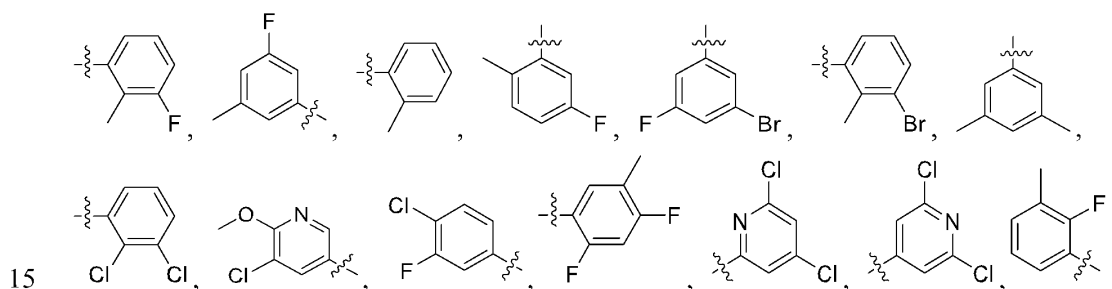
wherein R^{a1} and R^{a2} are independently selected from H, CN, F, Cl, Br, C_1 to C_4 alkyl, CF_3 , CF_2H , and OCH_3 , R^{a3} is H, or C_1 to C_4 alkyl, R^{a4} is selected from H, F, Cl, Br, and C_1 to C_4 alkyl, and X_1 and X_2 are independently selected from N, O, and S.

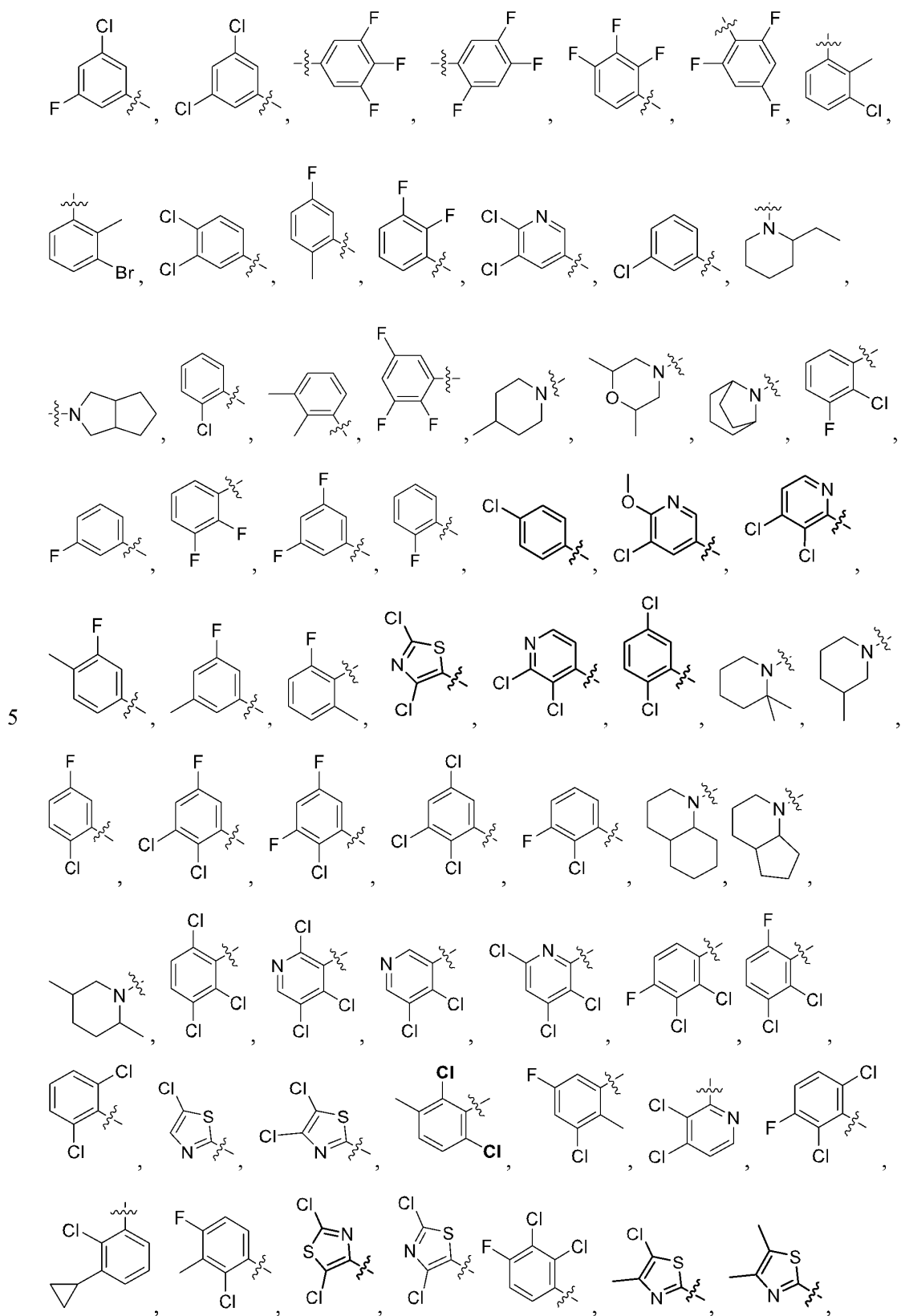
- 5 **46.** The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of claims 1 and 40, wherein Ring A is selected from:

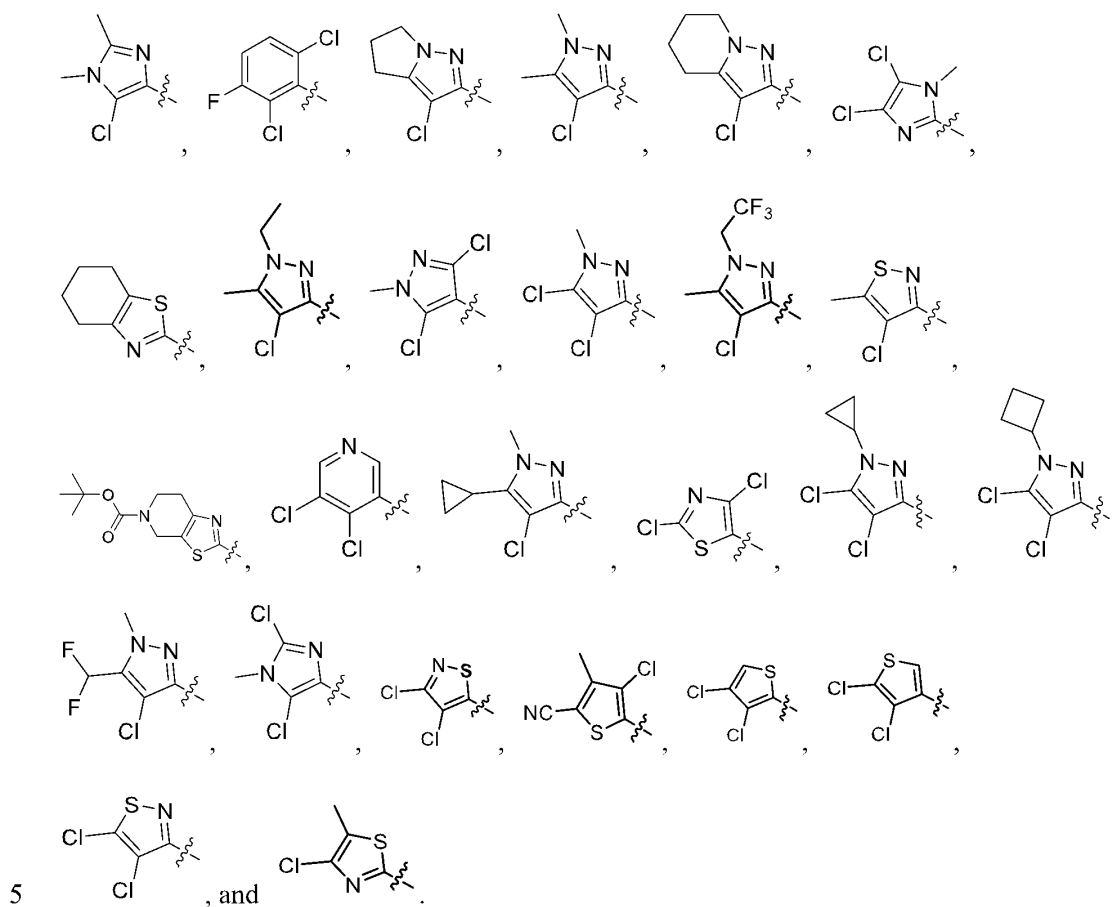


10 and R^{a1} , R^{a2} , R^{a3} , and R^{a4} are independently selected from H, CN, F, Cl, Br, C_1 to C_4 alkyl, CF_3 , CF_2H , and OCH_3 , R^{a3} is H, or C_1 to C_4 alkyl, R^{a4} is selected from H, F, Cl, Br, and C_1 to C_4 alkyl, and X_1 and X_2 are independently selected from N, O, and S.

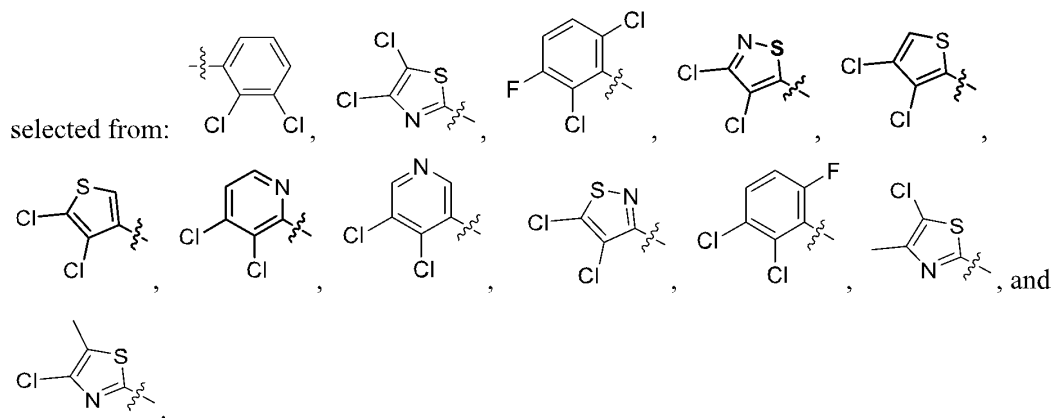
- 47.** The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of claims 1, 40, and 46, wherein Ring A substituted with m groups of R^a is selected from:



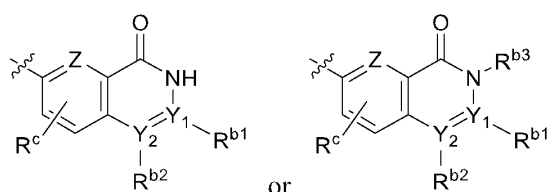




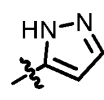
48. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of claims 1, 40, and 46-47, wherein Ring A substituted with m groups of R^a is

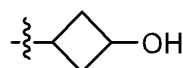


49. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of claims 1, 39, and 44-48, wherein Ring B substituted with n groups of R^b is:

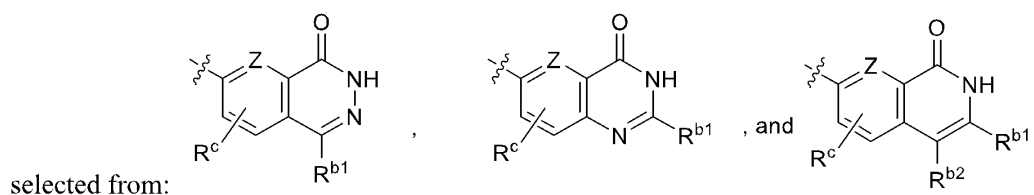


or , wherein Z is selected from C and N, Y₁ and Y₂ are independently selected from C and N, R^{b1} and R^{b2} are independently selected from H, F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, cyclopropyl, and OCH₃, wherein R^{b1} and R^{b2} are absent

when connected to N in Ring B, and R^{b3} is selected from H, methyl, ethyl, ,

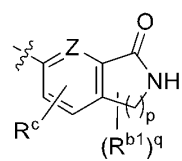
5 , and 5-membered heteroaryl, wherein the 5-membered heteroaryl of R^{b3} contains 2 to 3 heteroatoms selected from N and S and the 5-membered heteroaryl is optionally substituted with 1-2 groups selected from halogen and C₁ to C₄ alkyl, and R^c is selected from H, halogen, CN, and methyl.

50. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of claims 1, 39, and 44-49, wherein Ring B substituted with n groups of R^b is



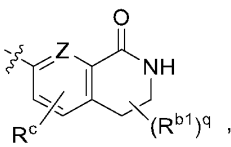
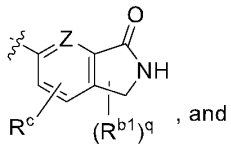
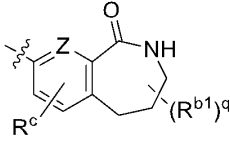
selected from: wherein Z is selected from C and N, R^{b1} is selected from H, F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, cyclopropyl, and OCH₃, R^{b2} is selected from H, F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, cyclopropyl, and OCH₃, and R^c is selected from H, halogen, CN, and methyl.

15 51. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of claims 1, 39 and 44-48, wherein Ring B substituted with n groups of R^b is:



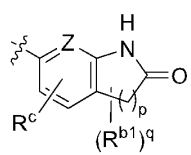
, wherein Z is selected from C and N, R^{b1} is selected from F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, cyclopropyl, and OCH₃, R^c is selected from H, halogen, CN, and methyl, p is 1, 2, or 3, and q is 0, 1, or 2.

20 52. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of claims 1, 39, 44-48, and 51, wherein Ring B substituted with n groups of R^b

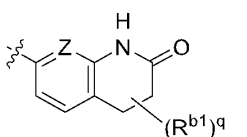
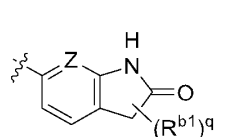
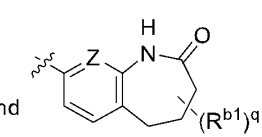
is selected from: , , and , wherein

Z is selected from C and N, R^{b1} is selected from F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, cyclopropyl, and OCH₃, R^c is selected from H, halogen, CN, and methyl, and q is 0, 1 or 2.

53. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of claims 1, 39, and 44-48, wherein Ring B substituted with n groups of R^b is:

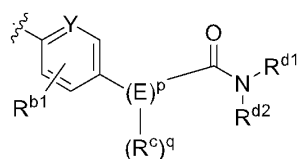
, wherein Z is selected from C and N, R^{b1} selected from F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, cyclopropyl, and OCH₃, R^c is H, halogen, CN, or methyl, p is 1, 2 or 3, q is 0, 1, or 2.

54. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of claims 1, 39, 44-48, and 53, wherein Ring B substituted with n groups of R^b

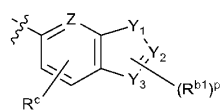
is selected from: , , and ,

wherein Z is selected from C and N, R^{b1} selected from F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, cyclopropyl, and OCH₃, and q is 0, 1 or 2.

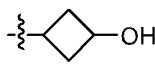
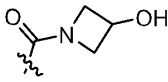
55. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of claims 1, 39, and 44-48, wherein Ring B substituted with n groups of R^b is

, wherein Y is selected from C and N, E is selected from C, N, and O, R^{d1} and R^{d2} are independently selected from H, methyl, ethyl, and cyclopropyl, R^c is selected from F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, cyclopropyl, and OCH₃, R^{b1} is selected from H, halogen, CN, and methyl, p is 1 or 2, and q is 0, 1, or 2.

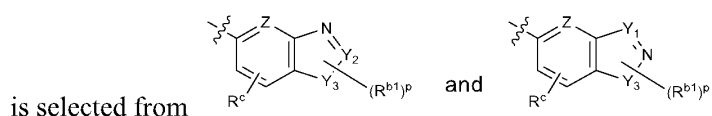
56. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of claims 1, 39, and 44-48, wherein Ring B substituted with n groups of R^b is



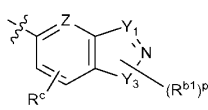
, wherein Z is selected from C and N, Y₁, Y₂, and Y₃ are independently selected from C, N, S, and O, R^{b1} is selected from F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl,

cyclopropyl, CONH₂, OCH₃, CH₂CONH₂, , and , R^c is selected from H, halogen, CN, and methyl, and p is 0, 1, or 2.

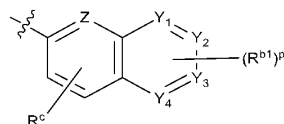
- 5 **57.** The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of claims 1, 39, 44-48, and 56, wherein Ring B substituted with n groups of R^b



is selected from

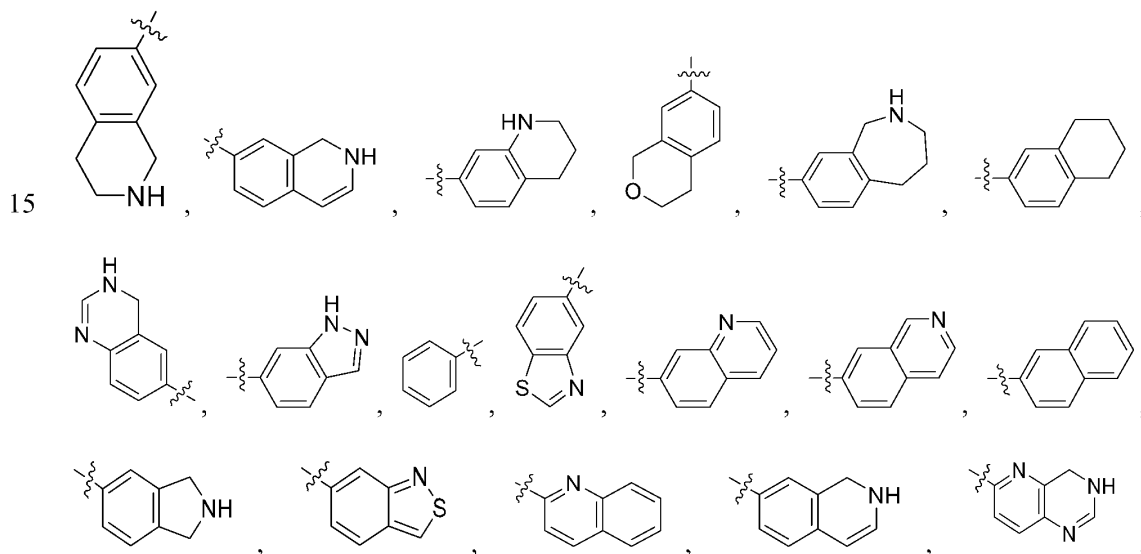


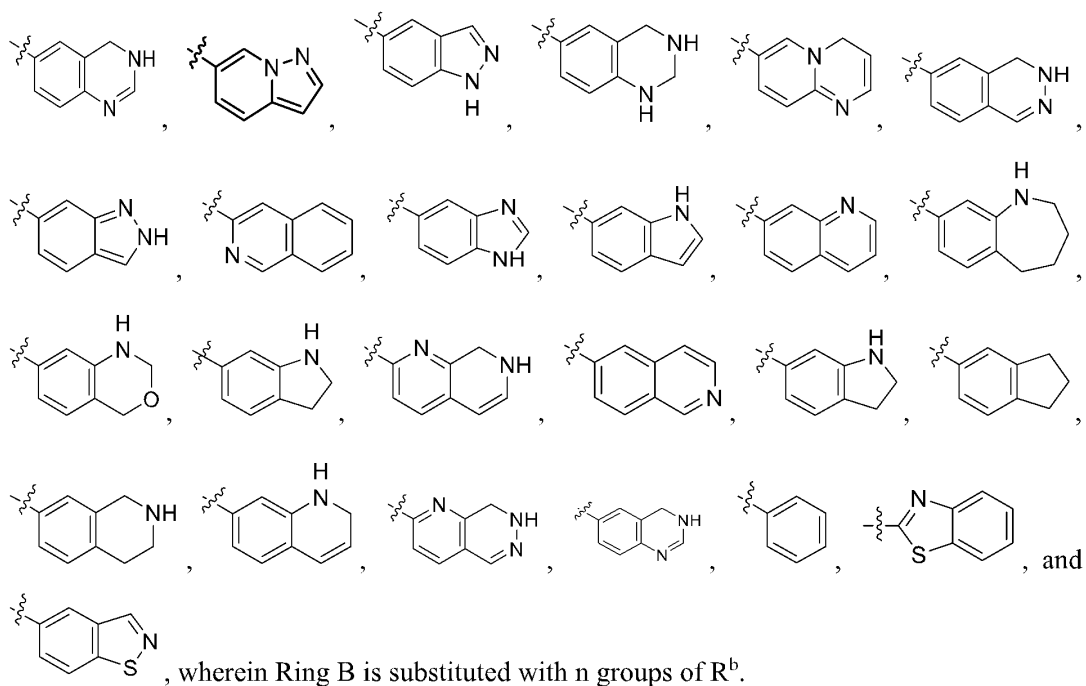
58. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of claims 1, 39, and 44-48, wherein Ring B substituted with n groups of R^b is



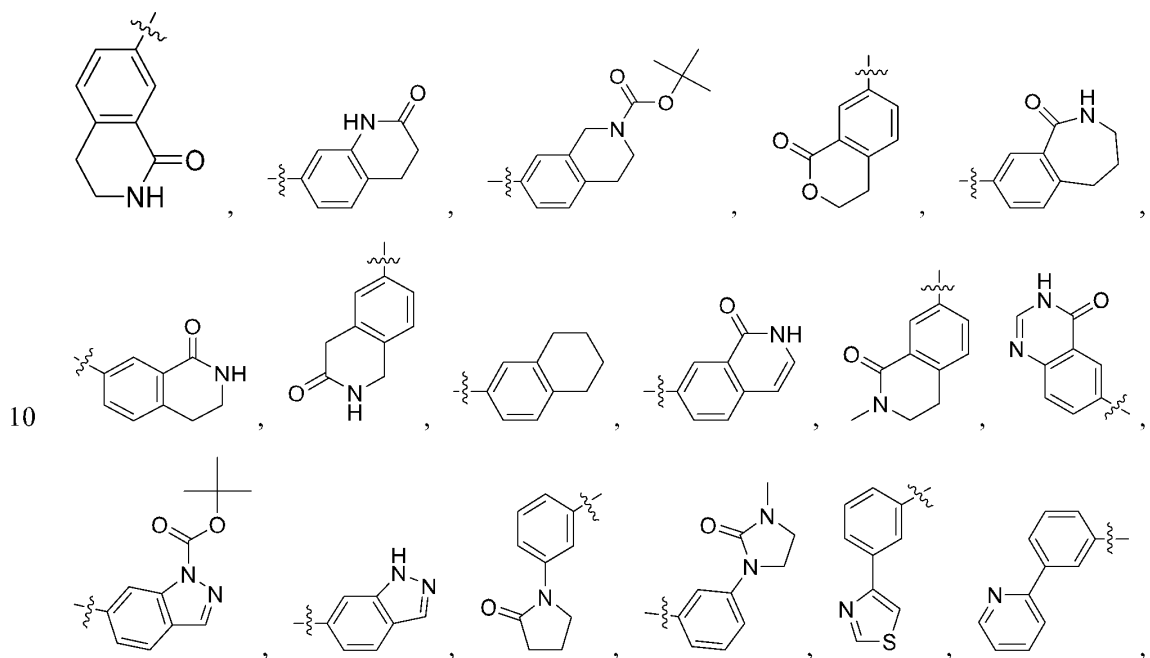
- 10 , Z is selected from C and N, Y₁, Y₂, Y₃, and Y₄ are independently selected from C and N, R^{b1} is selected from F, Cl, Br, methyl, CN, CF₃, CF₂H, ethyl, cyclopropyl, CONH₂, and OCH₃, R^c is H, halogen, CN, or methyl, and p is 0, 1, or 2.

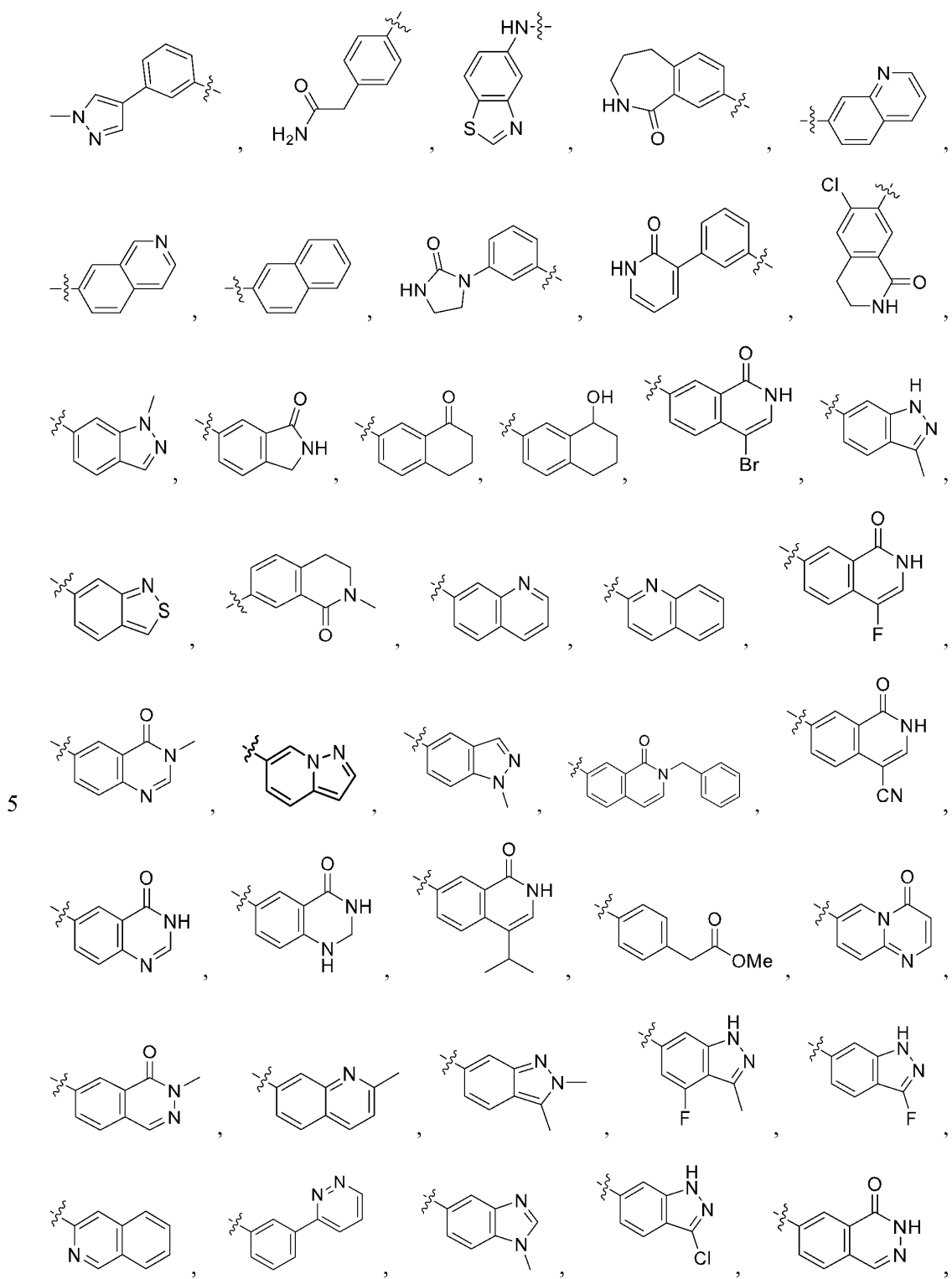
59. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of claims 1, 39, and 44-48, wherein Ring B is selected from:

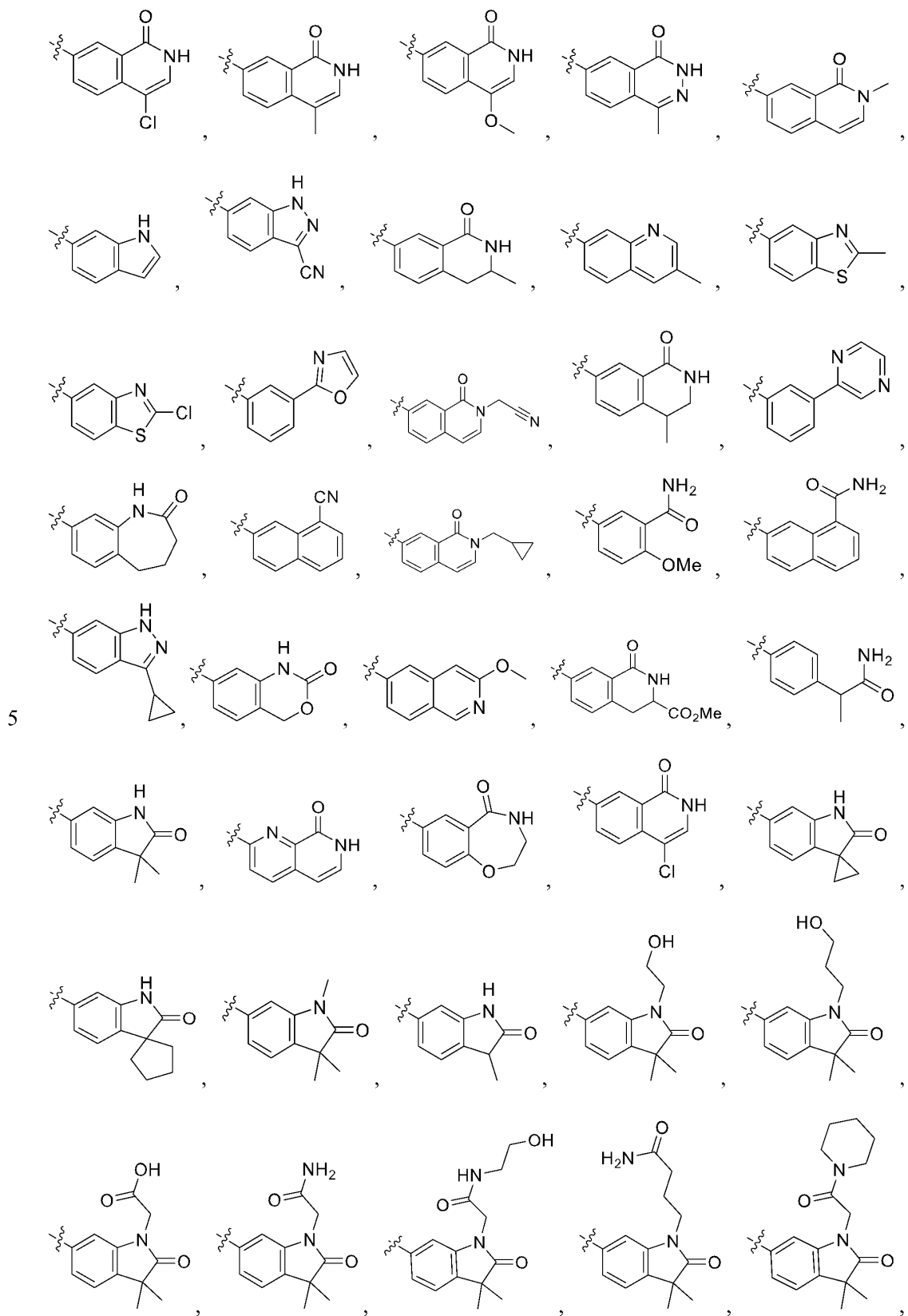


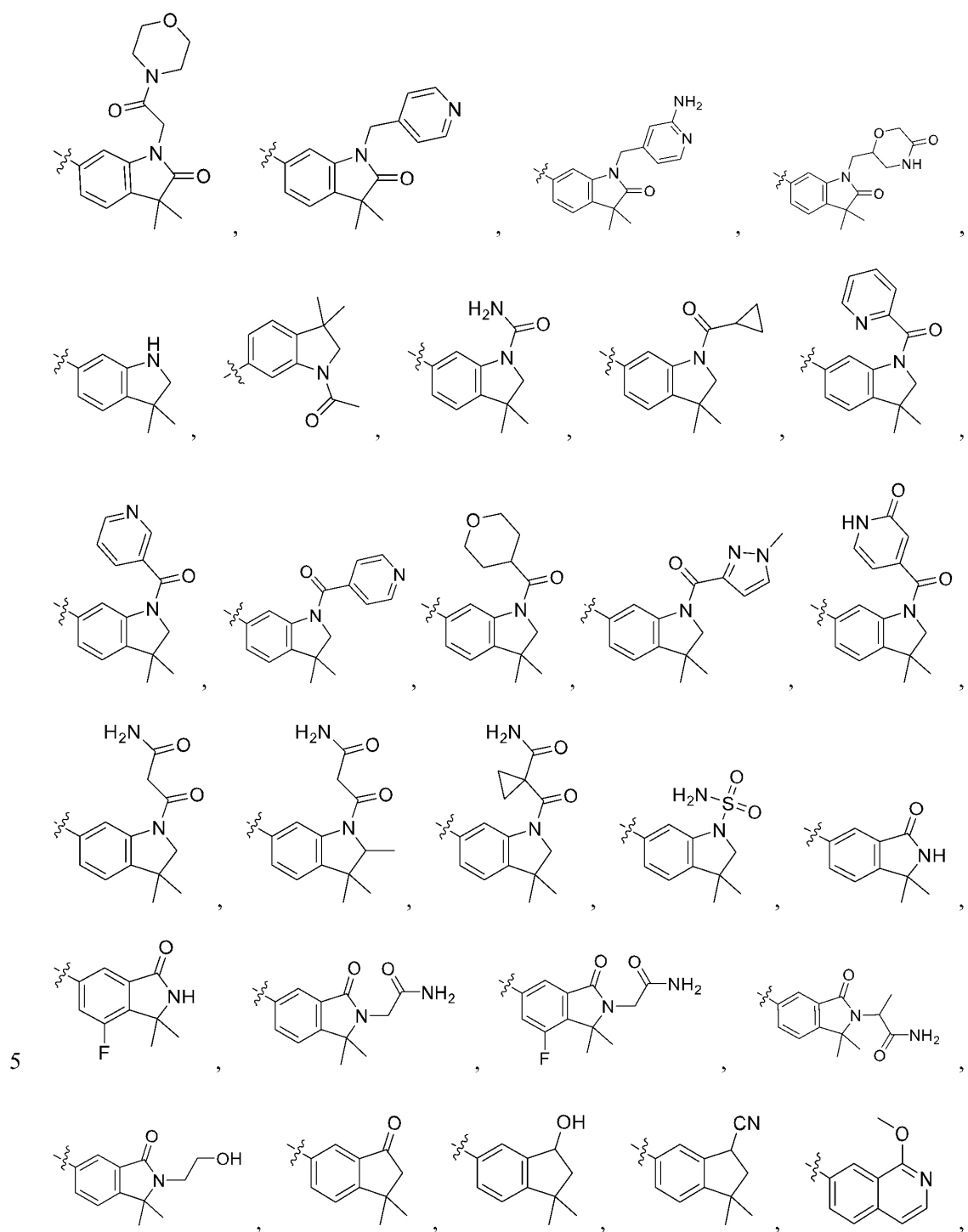


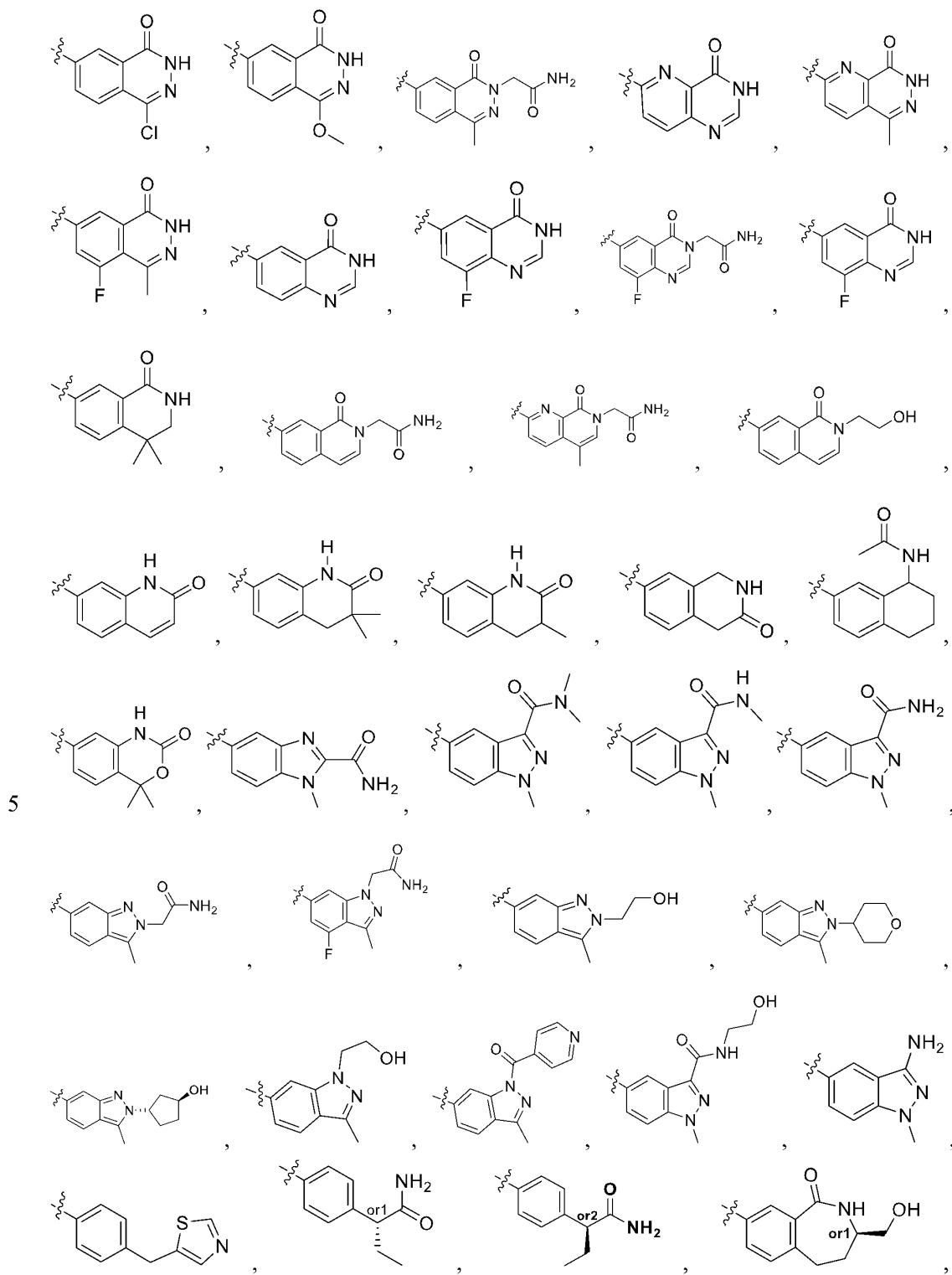
60. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of claims 1, 39, 44-48, and 59, wherein Ring B substituted with n groups of R^b is selected from:

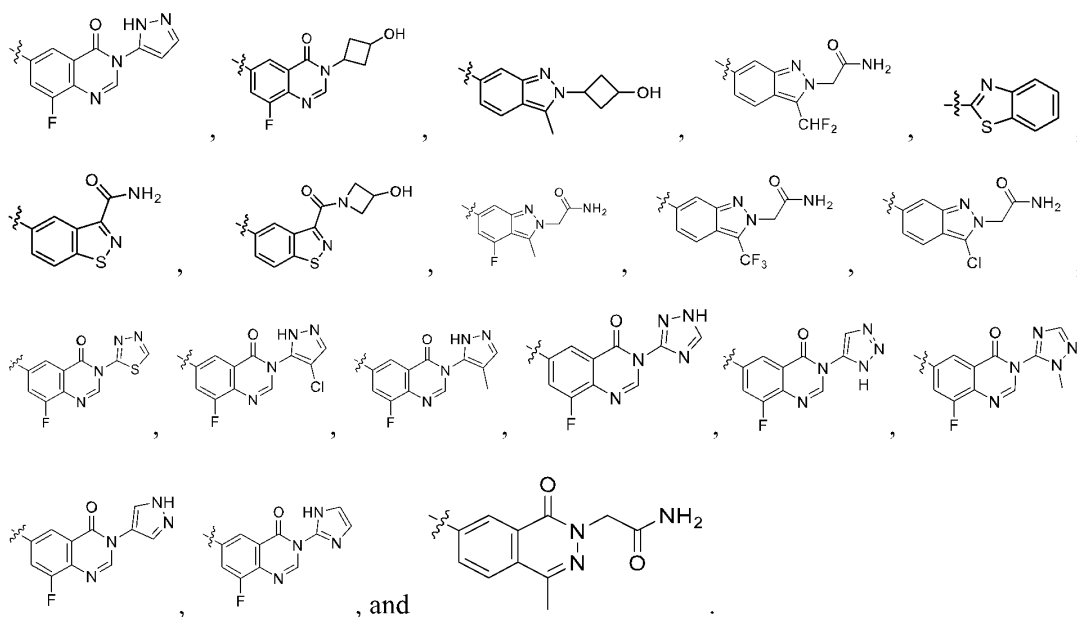




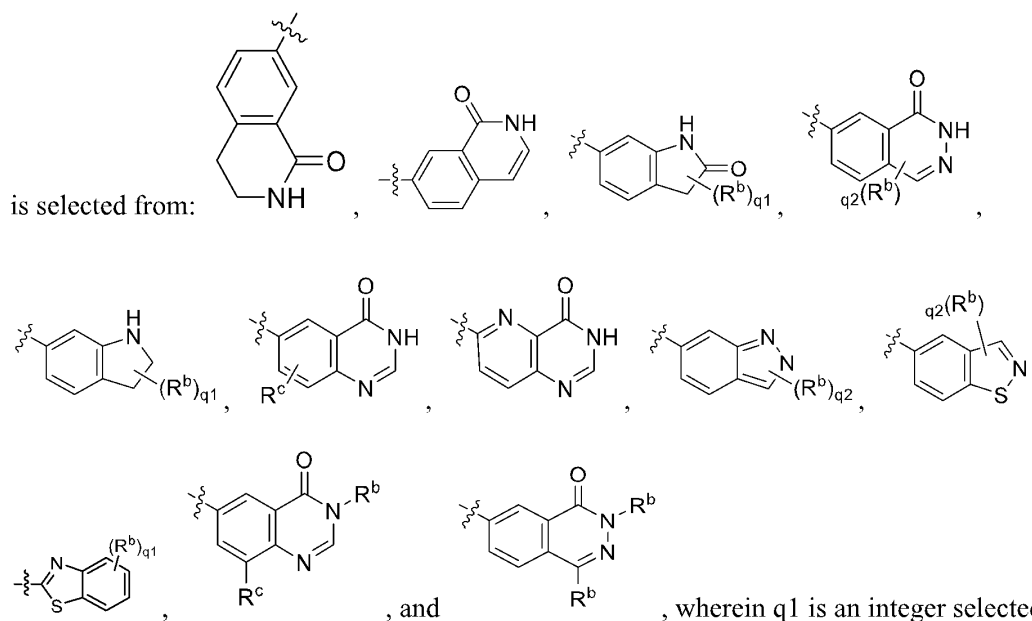








- 5 **61.** The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of claims 1, 39, 44-48, and 59, wherein Ring B substituted with n groups of R^b



- 10 from 0, 1, 2, and 3, q_2 is an integer selected from 0, 1, and 2, and R^c is selected from F, Cl, Br and Me.

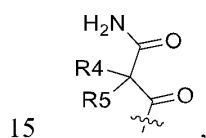
- 62.** The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of claims 1, 39, 40, and 46, wherein R^a is selected from C_3 - C_5 cycloalkyl, - O (C_1 - C_2 alkyl), $COOH$, CN , $CONH_2$, $-C(=O)NH(C_1-C_2$ alkyl), $-C(=O)N(C_1-C_2$ alkyl) $_2$, -

C(=O)O(C₁-C₂ alkyl), halogen, and C₁-C₂ alkyl optionally substituted with 1 to 3 groups selected from halogen.

- 63.** The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of claims 1, 39, 40, 46, and 62, wherein R^a is selected from CH₃, CH₂CH₃,
 5 CH₂CF₃, F, Cl, Br, C₃-C₄ cycloalkyl, COOH, CN, CONH₂, -C(=O)NHCH₃, -C(=O)NCH₃, -OC(=O)N(CH₃)₃, and OCH₃.

- 64.** The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of claims 1, 39, 40, 44-48, 59, and 62-63, wherein R^b is selected from =O, OH,
 halogen, CN, -C(=O)NH(C₁-C₄ alkyl), -C(=O)O(C₁-C₄ alkyl), -C(=O)NH₂,
 10 C₃-C₄ cycloalkyl optionally substituted with OH,

O(C₁-C₃ alkyl), -C(=O)(C₁-C₂ alkyl), -C(=O)(C₃-C₆ cycloalkyl), -C(=O)(4- to 6-membered heterocyclyl optionally substituted with =O), -C(=O)(5- to 6-membered heteroaryl optionally substituted with C₁-C₂ alkyl or NH₂), -C(=O)(CH₂)_pC(=O)NH₂, -NHC(=O)(C₁-C₂ alkyl), -C(=O)N(C₁-C₂ alkyl)₂, -C(=O)NH(CH₂)_pOH, -S(=O)₂NH₂,



- C₁-C₃ alkyl optionally substituted with 1 to 3 groups selected from halogen, NH₂, OH, OCH₃, -C(=O)NH(C₁-C₄ alkyl), -C(=O)O(C₁-C₄ alkyl), -C(=O)N(C₁-C₄ alkyl)₂, -COOH, -C(=O)NH₂, CN, C₃-C₄ cycloalkyl, phenyl, -C(=O)(C₁-C₂ alkyl), -C(=O)(C₃-C₆ cycloalkyl), -C(=O)(5- to 6-membered heterocyclyl), -C(=O)(5- to 6-membered heteroaryl optionally
 20 substituted with C₁-C₂ alkyl), C(=O)NH(CH₂)_pOH, and 5- to 6-membered heteroaryl,

5- to 6- membered heteroaryl optionally substituted with 1 to 2 groups selected from C₁-C₂ alkyl, and

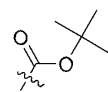
5- to 6-membered heterocyclyl optionally substituted with 1 to 2 groups selected from =O and C₁-C₂ alkyl, or

- 25 two R^b attached to the same position on Ring B join to form a C₃-C₅ cycloalkyl,

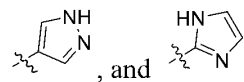
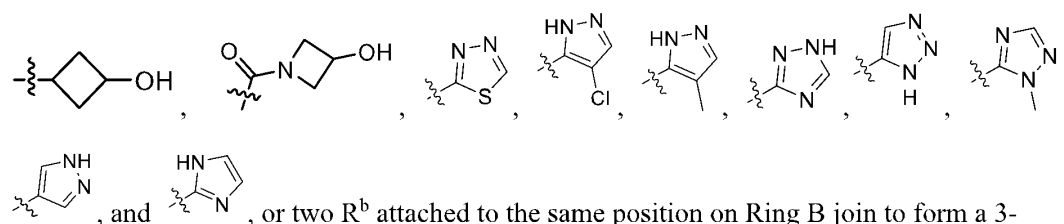
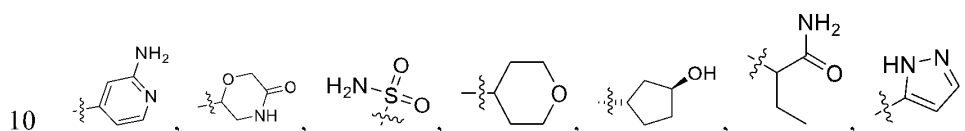
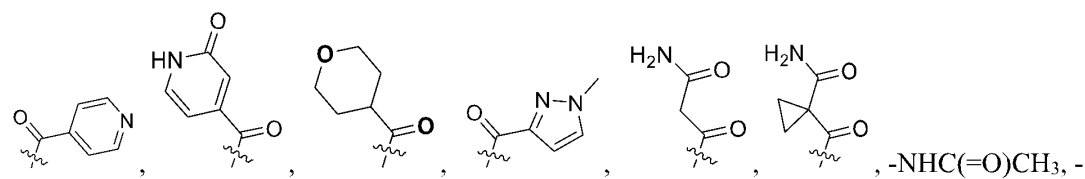
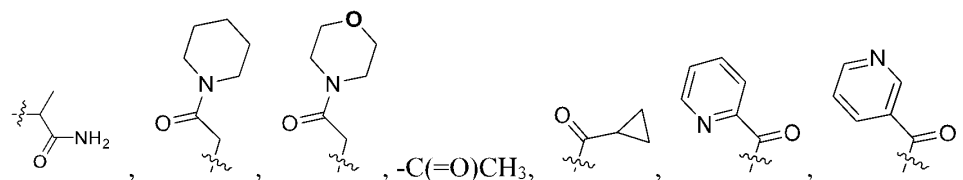
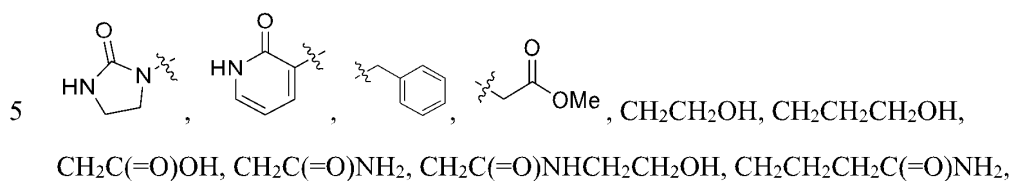
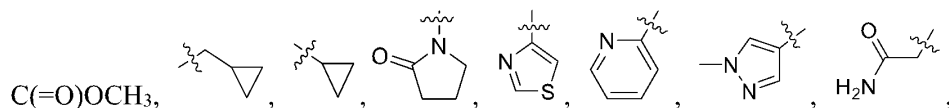
wherein p is an integer selected from 1 and 2, and

wherein R₄ and R₅ are each independently selected from H and C₁ to C₃ alkyl or R₄ and R₅ join to form a 3 to 5-membered cycloalkyl.

65. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of claims 1, 39, 40, 44-48, 59, and 62-64, wherein R^b is selected from =O,

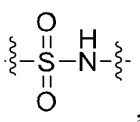


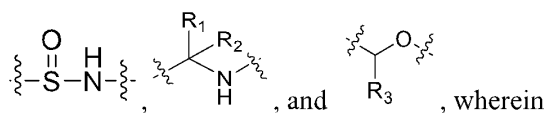
, CH₃, CHF₂, CF₃, OH, F, Cl, Br, CN, CH(CH₃)₂, CH₂CN, OCH₃, -C(=O)NH₂, -



membered or 5-membered cycloalkyl.

66. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable

salt of any one of claims 1, 13, 15, 17, and 25-65, wherein L is selected from ,



R₁ is H, D or C₁-C₄ alkyl, and R₂ is selected from CN, C₁-C₄ alkenyl, C₃-C₅ cycloalkyl, 5 to 6-membered heteroaryl,

5 phenyl optionally substituted with 1 to 2 groups selected from C₁-C₃ alkyl and halogen, and

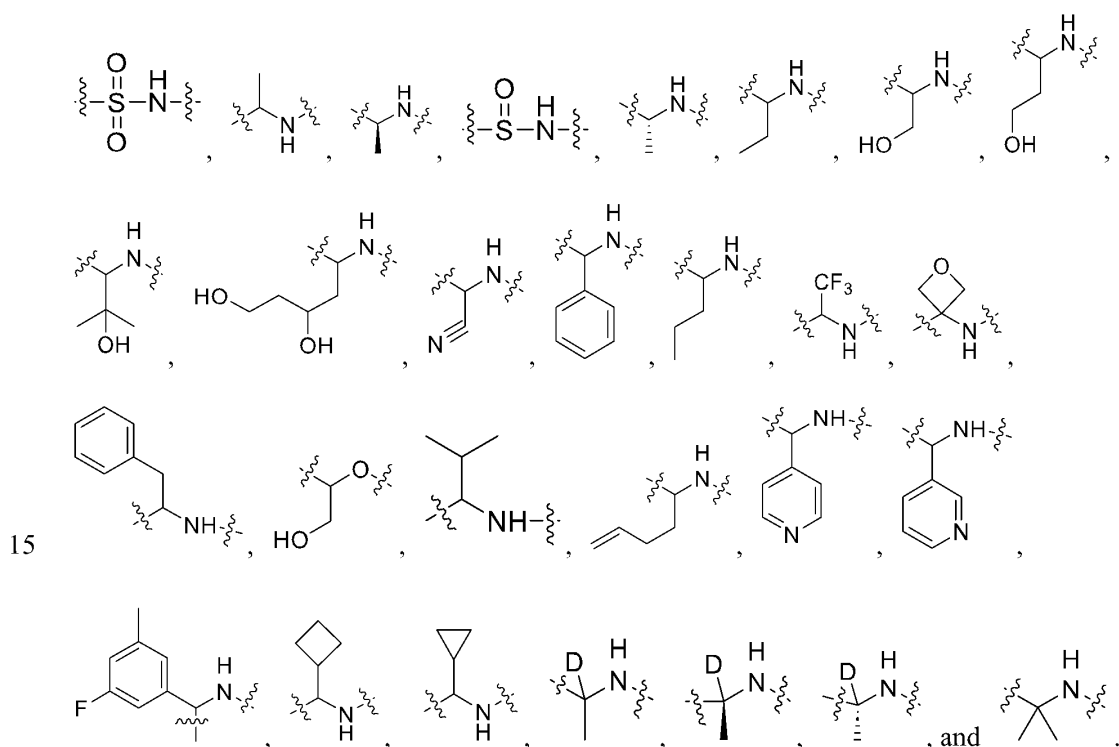
C₁-C₄ alkyl optionally substituted with 1 to 3 groups selected from halo, OH, and phenyl,

or

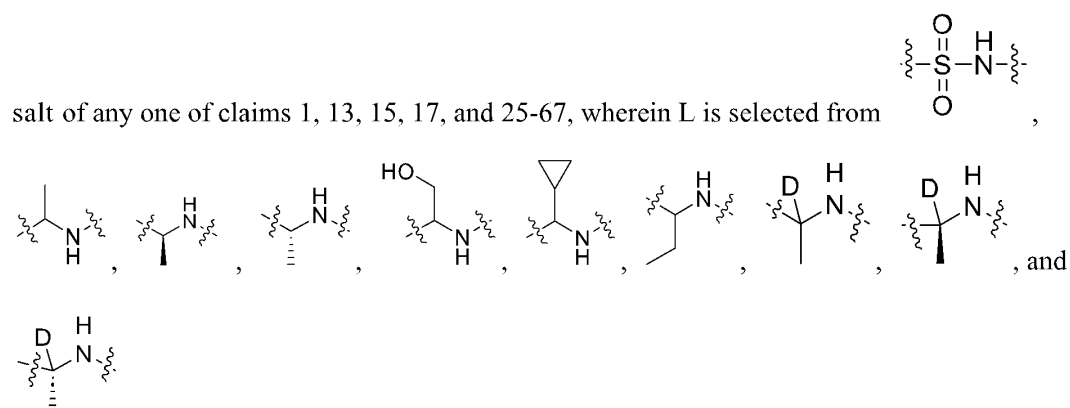
R₁ and R₂ join to form a 3-4 membered heterocyclyl; and

10 R₃ is C₁-C₄ alkyl optionally substituted with 1 to 3 groups selected from halogen and OH.

67. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of claims 1, 13, 15, 17, and 25-66, wherein L is selected from

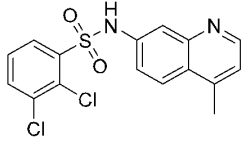
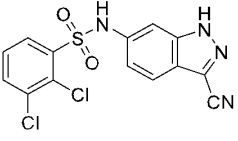
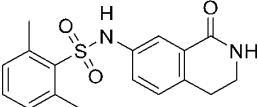
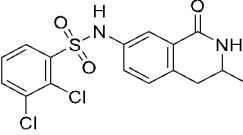
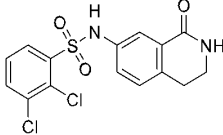
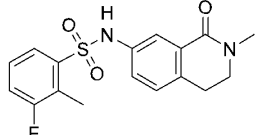
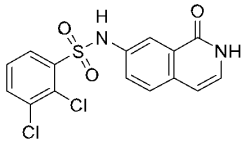
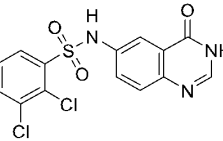
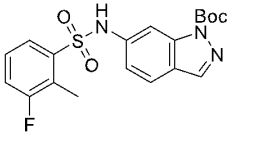
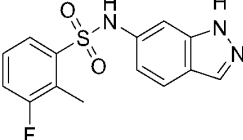
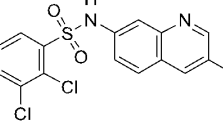
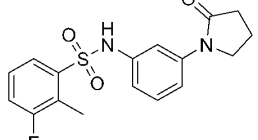
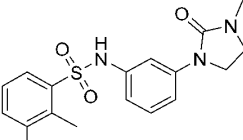
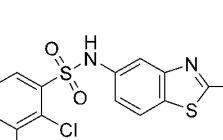
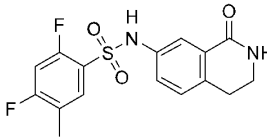
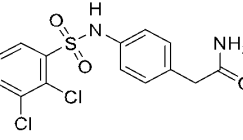
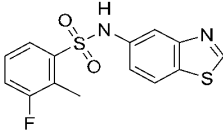
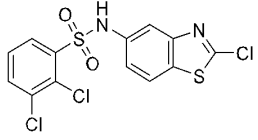
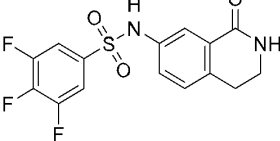
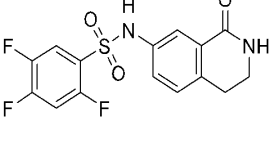
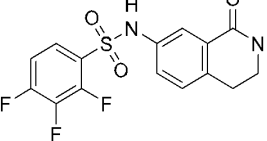
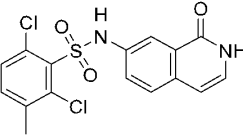
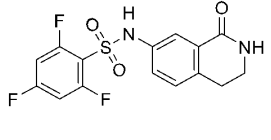
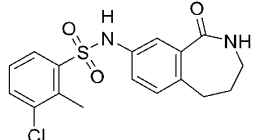


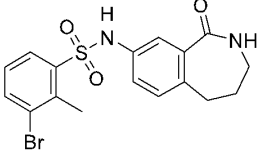
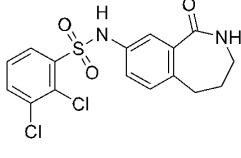
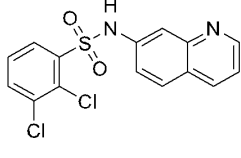
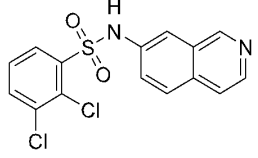
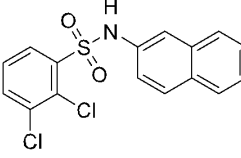
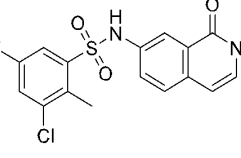
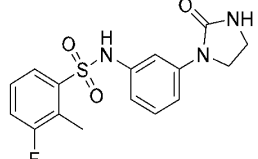
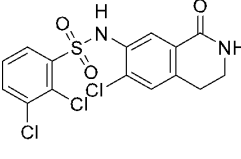
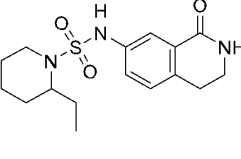
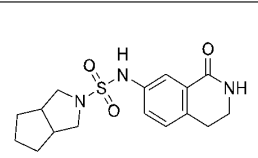
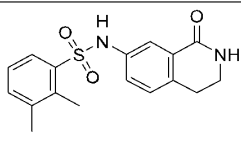
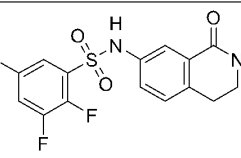
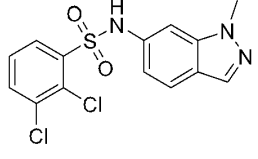
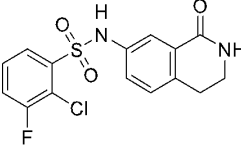
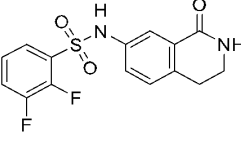
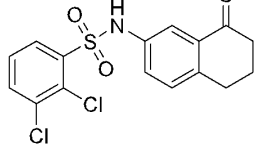
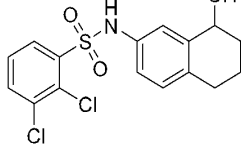
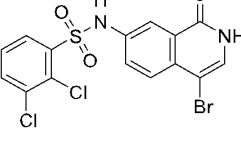
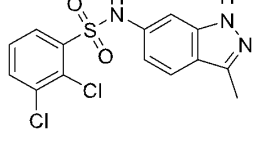
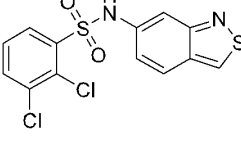
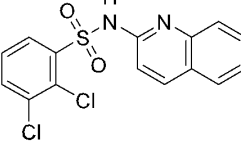
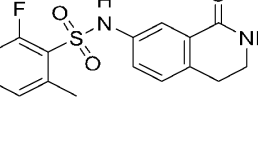
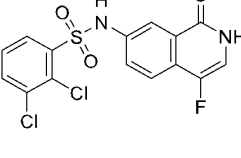
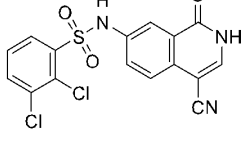
68. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable

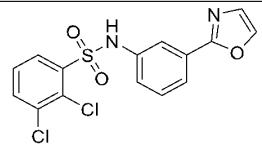
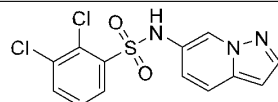
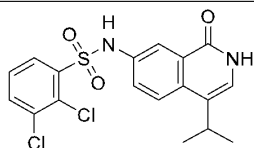
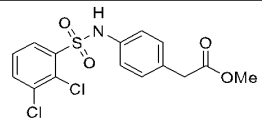
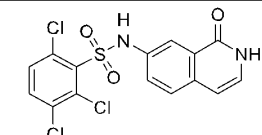
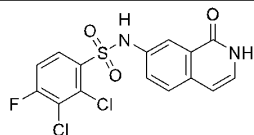
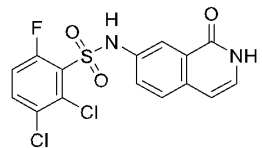
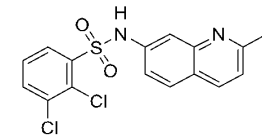
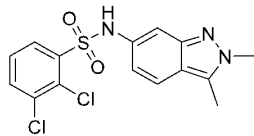
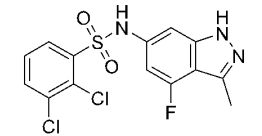
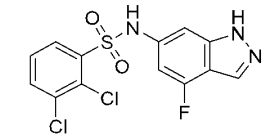
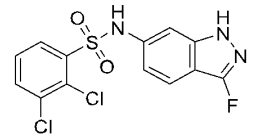
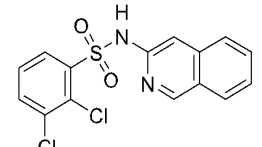
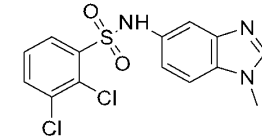
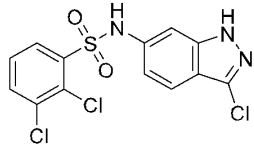
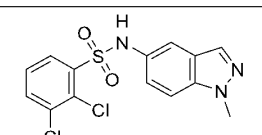
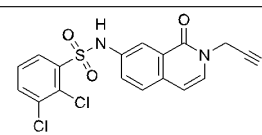
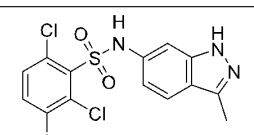
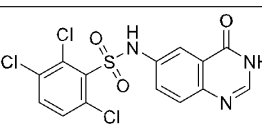
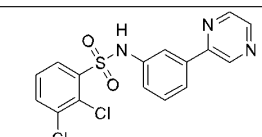
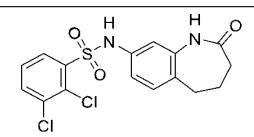
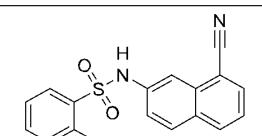
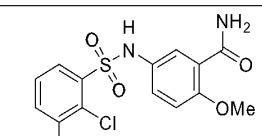
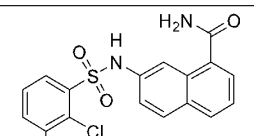
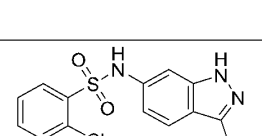
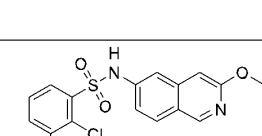
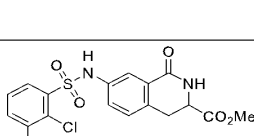


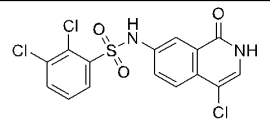
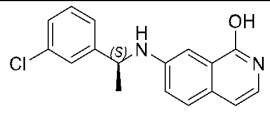
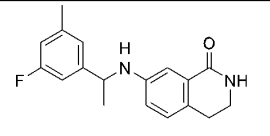
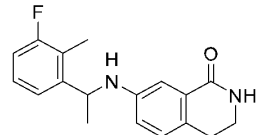
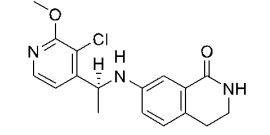
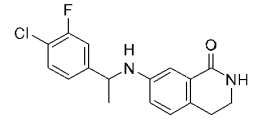
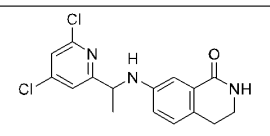
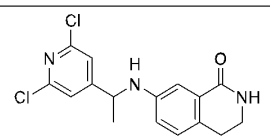
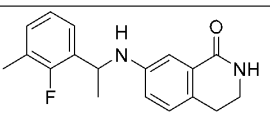
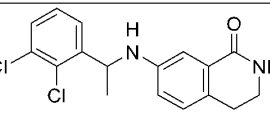
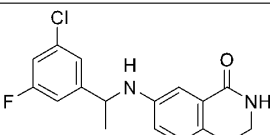
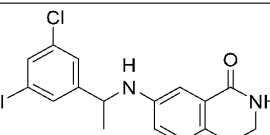
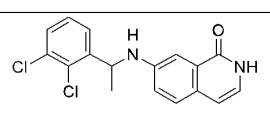
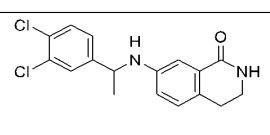
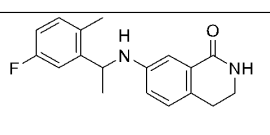
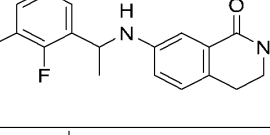
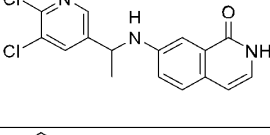
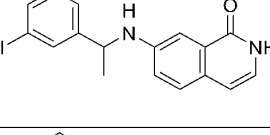
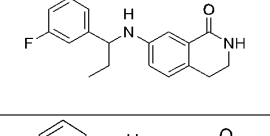
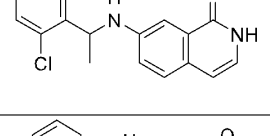
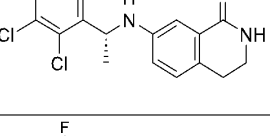
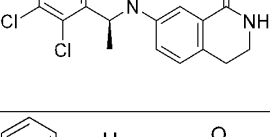
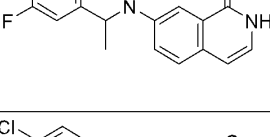
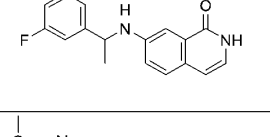
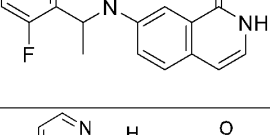
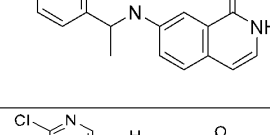
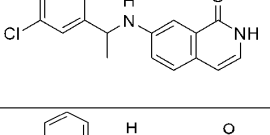
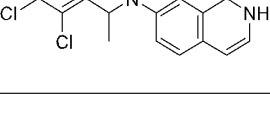
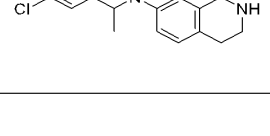
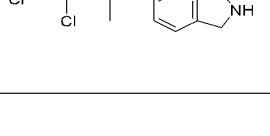
69. The compound according to claim 1, wherein the compound is selected from

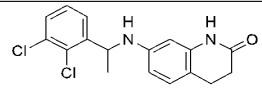
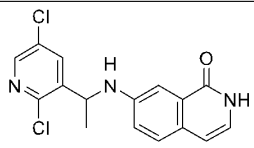
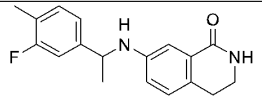
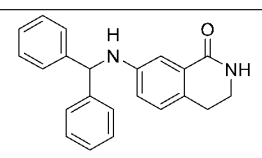
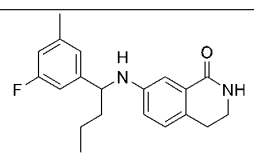
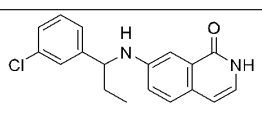
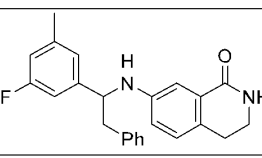
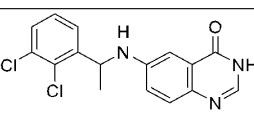
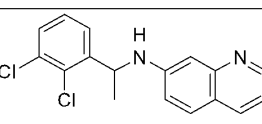
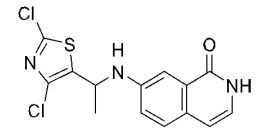
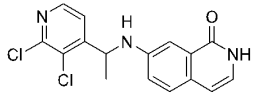
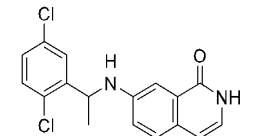
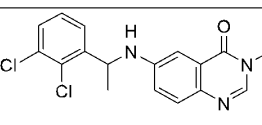
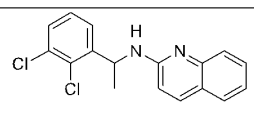
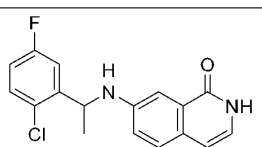
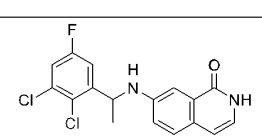
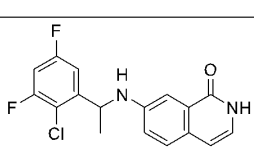
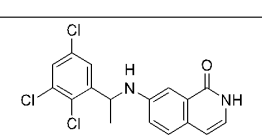
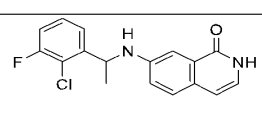
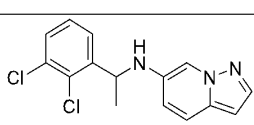
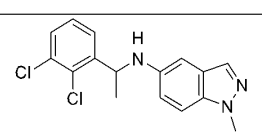
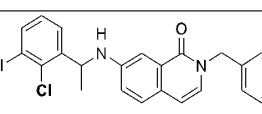
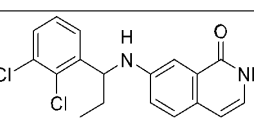
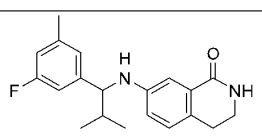
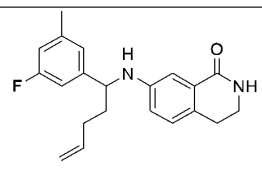
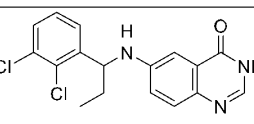
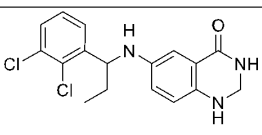
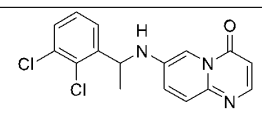
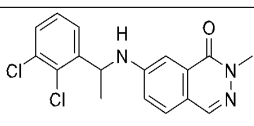
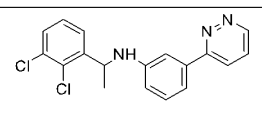
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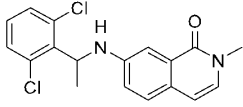
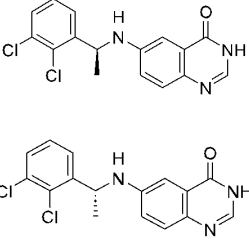
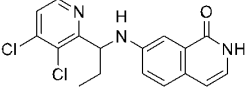
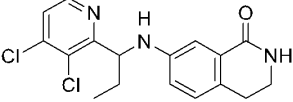
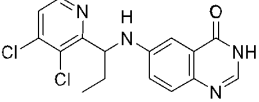
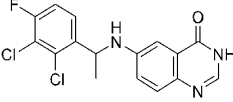
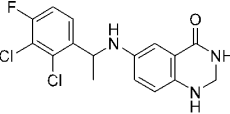
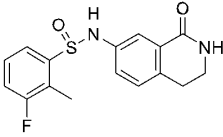
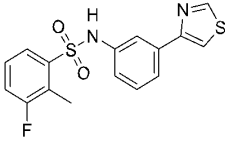
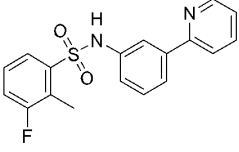
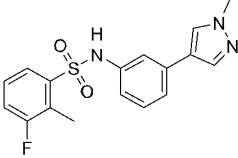
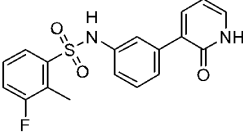
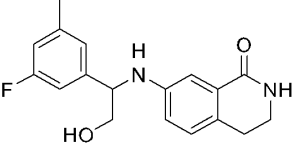
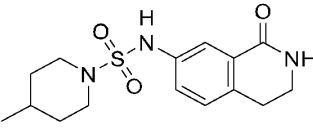
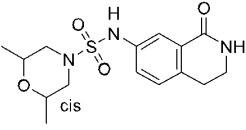
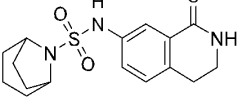
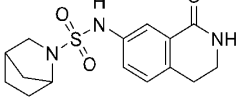
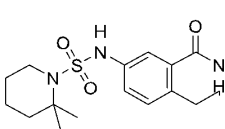
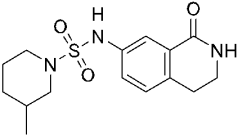
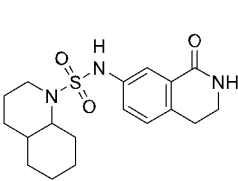
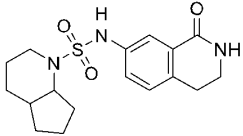
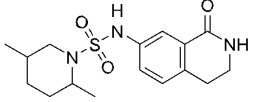
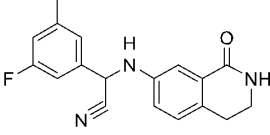
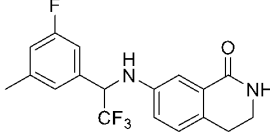
		
		
		
		
		
		
		
		

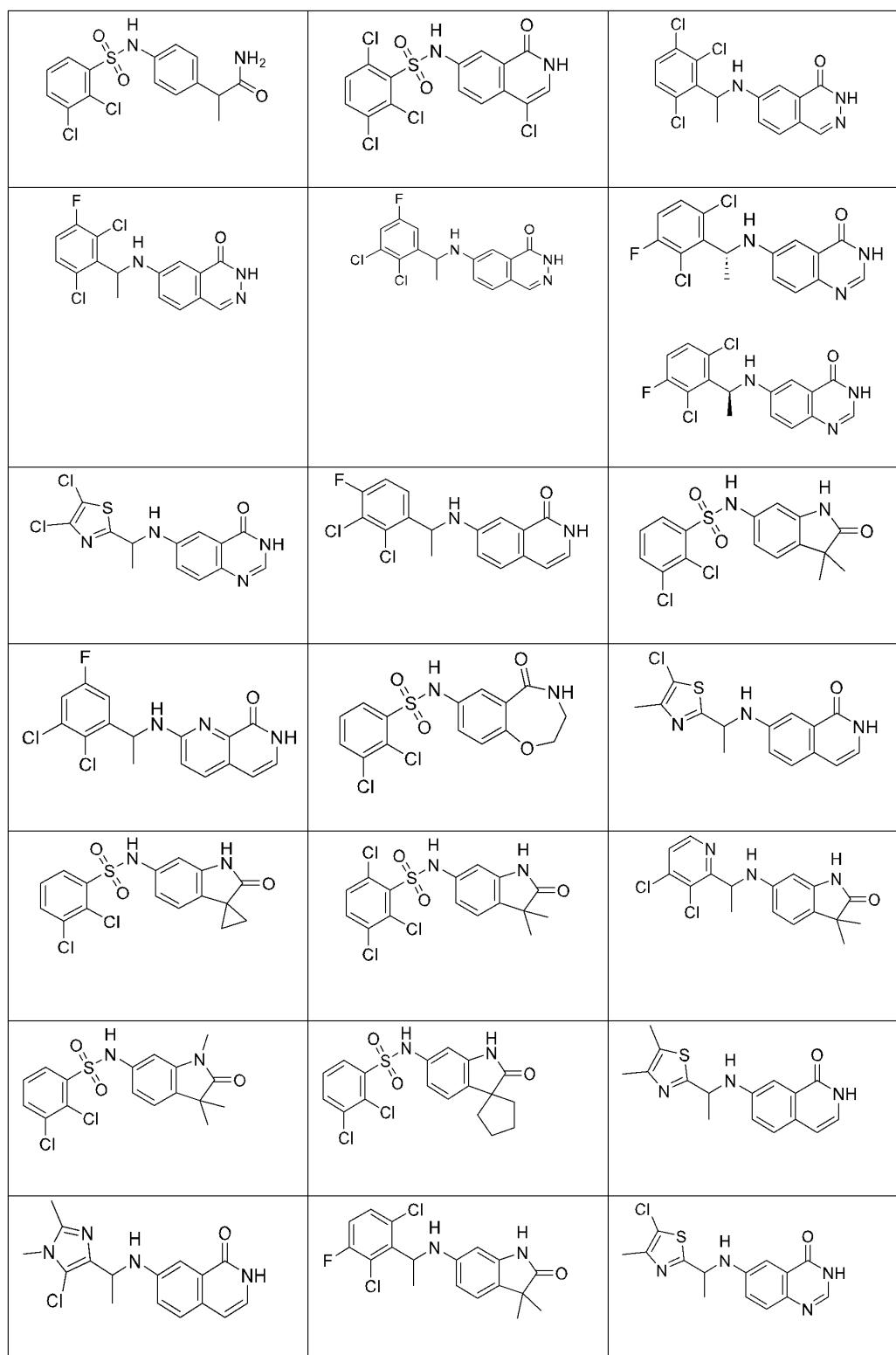
		
		
		
		
		
		
		
		

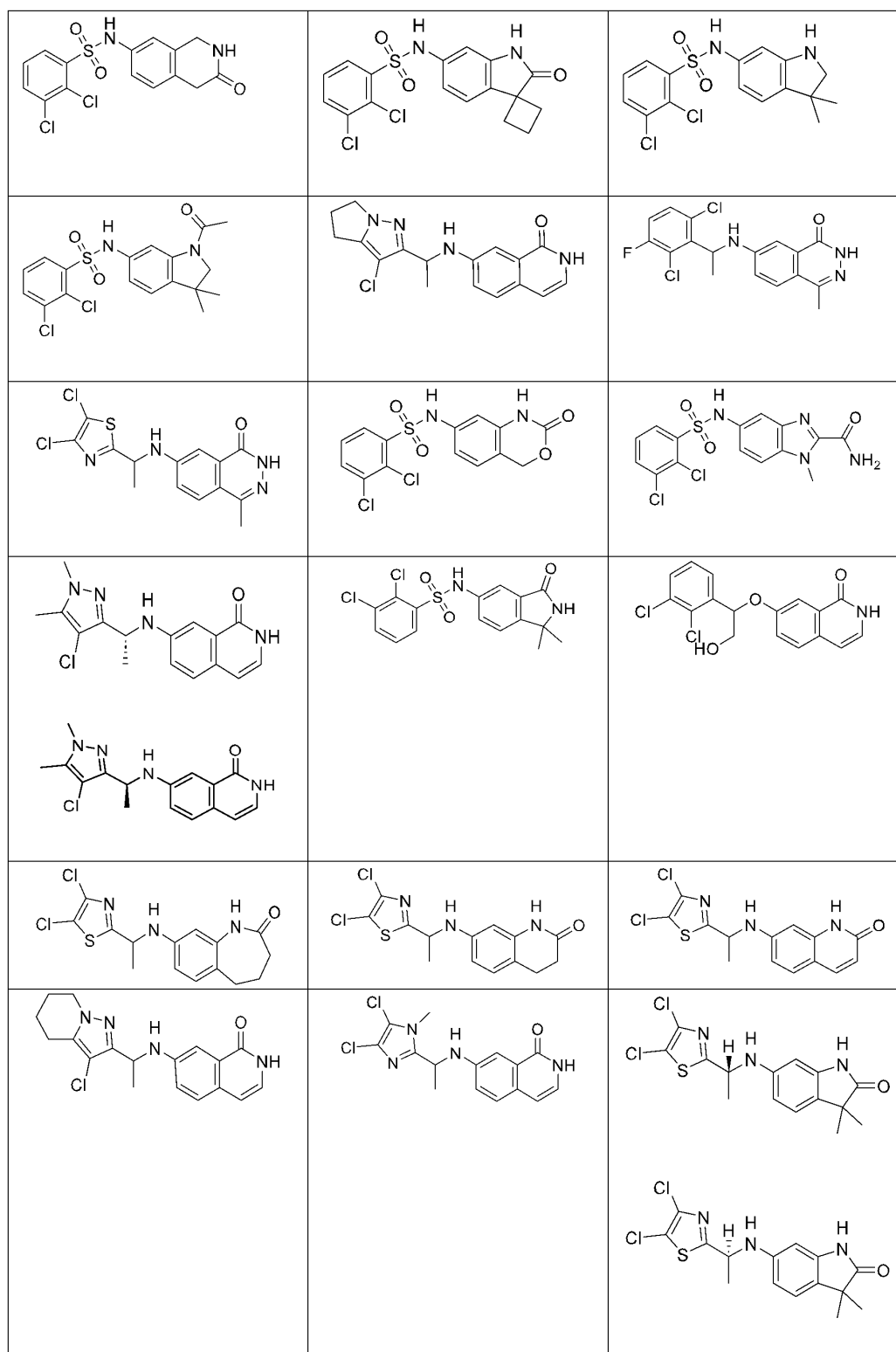
		
		
		
		
		
		
		
		
		

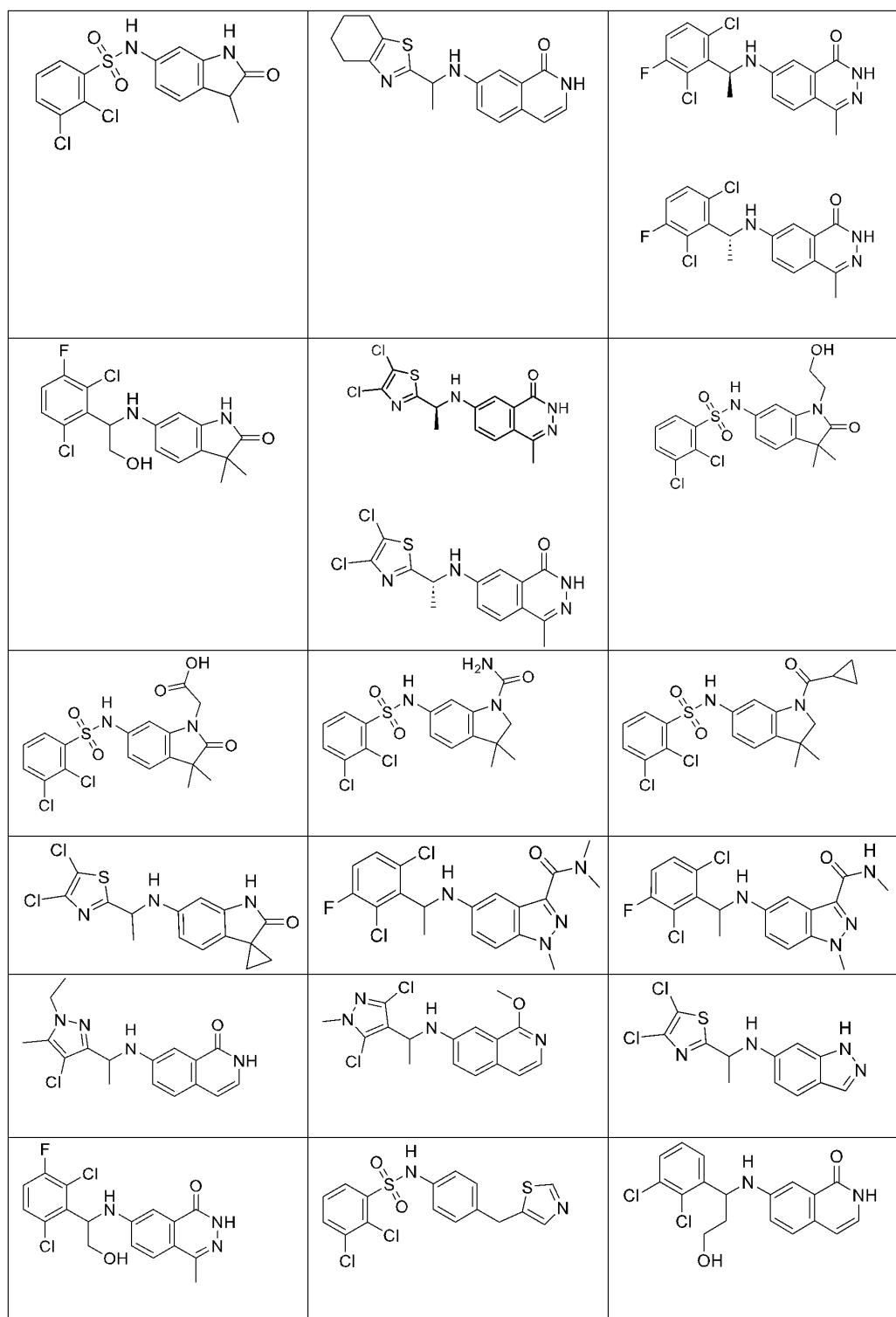
		
		
		
		
		
		
		
		
		
		

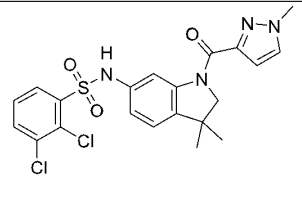
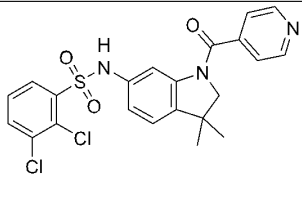
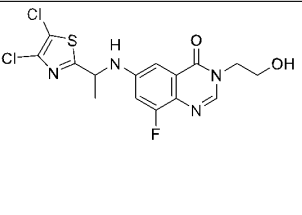
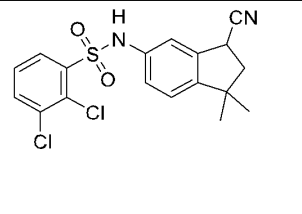
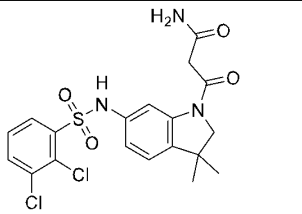
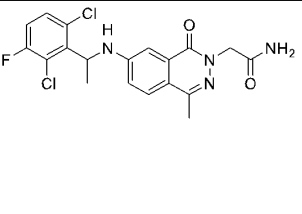
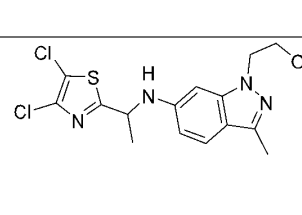
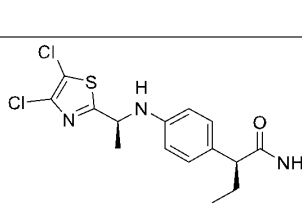
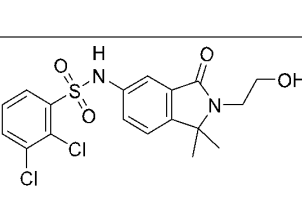
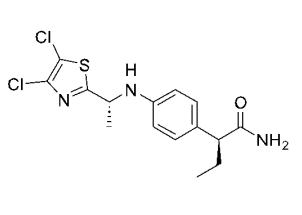
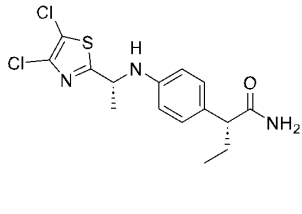
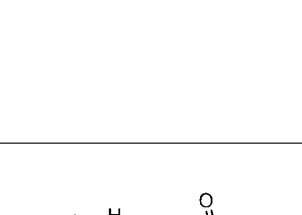
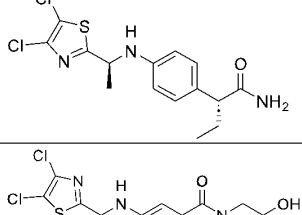
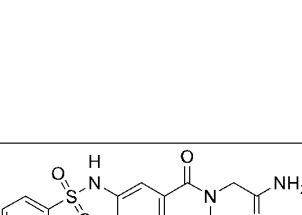
		
		
		
		
		
		
		
		
		
		

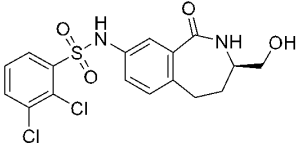
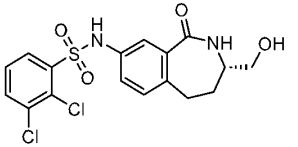
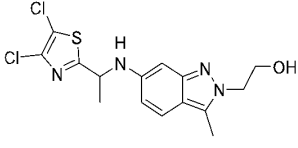
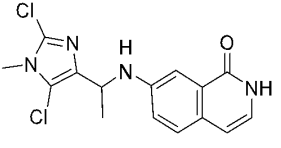
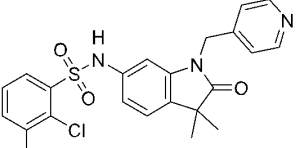
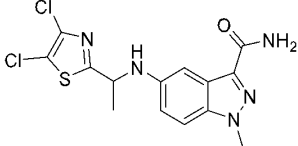
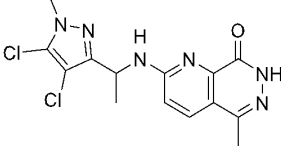
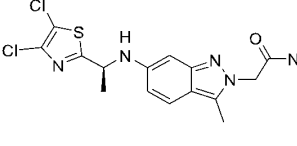
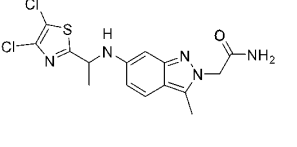
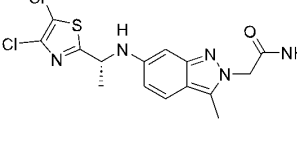
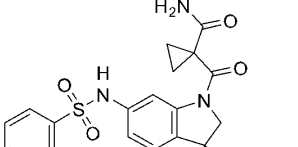
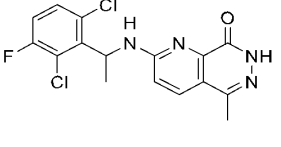
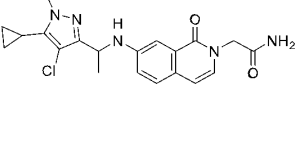
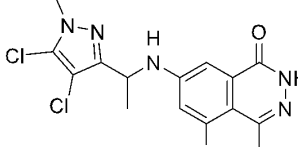
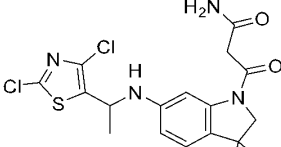
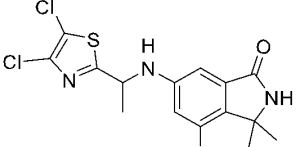
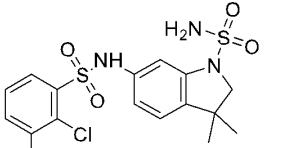
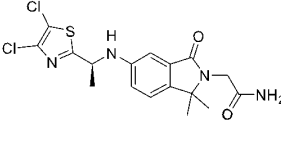
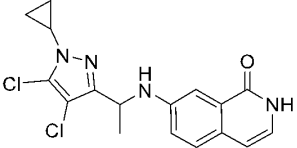
		
		
		
		
		
		
		
		









a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

70. A pharmaceutical composition comprising a compound according to any one of claims 1 to 69, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer,
5 or a pharmaceutically acceptable salt of the foregoing and at least one pharmaceutically acceptable carrier.

71. A method of treating a disease or condition, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound according to any one of claims 1 to 69 and Compounds 1A to 121A, a tautomer thereof, a solvate or
10 stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or the pharmaceutical composition according to claim 70, or a pharmaceutical composition comprising any one of Compounds 1A to 121A, wherein the disease or condition is selected from ALS, Parkinson's disease, multiple sclerosis, traumatic brain injury, diabetic neuropathy, and CIPN.

15 72. A method of treating a disease or condition caused by axonal degeneration, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound according to any one of claims 1 to 69 and Compounds 1A to 121A, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition
20 according to claim 70, or a pharmaceutical composition comprising any one of Compounds 1A to 121A.

73. A method of modulating SARM1, comprising contacting a subject in need thereof with a compound according to any one of claims 1 to 69 and Compounds 1A to 121A, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a
25 pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition according to claim 70, or a pharmaceutical composition comprising any one of Compounds 1A to 121A.

74. A method of inhibiting or preventing axonal degeneration, comprising contacting a subject in need thereof with a compound according to any one of claims 1 to 69 and Compounds 1A to 121A, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition according to claim 70, or a pharmaceutical composition comprising any one of Compounds 1A to 121A.