

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 May 2012 (18.05.2012)

(10) International Publication Number
WO 2012/064744 A2

(51) International Patent Classification:
A61K 31/538 (2006.01)

(21) International Application Number:

PCT/US2011/059788

(22) International Filing Date:

8 November 2011 (08.11.2011)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/411,084 8 November 2010 (08.11.2010) US

(71) Applicant (for all designated States except US): **LYC-ERA CORPORATION** [US/US]; 2800 Plymouth Rd., NCRC, Building 26, Ann Arbor, MI 48109 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **GLICK, Gary, D.** [US/US]; 1663 Snowberry Ridge Road, Ann Arbor, MI 48103 (US). **TOOGOOD, Peter, L.** [US/US]; 2281 Sun Valley Drive, Ann Arbor, MI 48108 (US). **ROMERO, Arthur, Glenn** [US/US]; 1201 Turnberry Ridge Ct., Chesterfield, MO 63005 (US). **VANHUIS, Chad, A.** [US/US]; 13850 Plover Drive, Hartland, MI 48353 (US). **AICHER, Thomas, Daniel** [US/US]; 162 Rockwood Court, Ann Arbor, MI 48103 (US). **KAUB, Carl** [US/US]; 40 West 4th Avenue, Unit 104, San Mateo, CA 94402 (US). **MATTSON, Matthew, N.** [US/US]; 3665 Benton Street, #84, Santa Clara, CA 85051 (US). **THOMAS, William, David** [US/US]; 1803 Charmeran Avenue, San Jose, CA 95124 (US). **STEIN, Karin, Ann** [US/US]; 1174 Nilda Avenue, Mountain View, CA 94040 (US). **KROGH-JESPERSEN, Erik** [US/US]; 2285 Saint

Francis Drive, Palo Alto, CA 94303 (US). **WANG, Zhan** [US/US]; 14610 Mount Herman Drive, San Jose, CA 95127 (US).

(74) Agents: **DAVIS, Chad, E.** et al.; Goodwin Procter LLP, Exchange Place, Boston, MA 02109 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report (Rule 48.2(g))



WO 2012/064744 A2

(54) Title: TETRAHYDROQUINOLINE AND RELATED BICYCLIC COMPOUNDS FOR INHIBITION OF RORY ACTIVITY AND THE TREATMENT OF DISEASE

(57) Abstract: The invention provides tetrahydroquinoline and related compounds, pharmaceutical compositions, methods of inhibiting RORY activity, reducing the amount of IL-17 in a subject, and treating immune disorders and inflammatory disorders using such tetrahydroquinoline and related compounds are provided.

TETRAHYDROQUINOLINE AND RELATED BICYCLIC COMPOUNDS FOR INHIBITION OF ROR γ ACTIVITY AND THE TREATMENT OF DISEASE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to United States Provisional Patent Application serial number 61/411,084, filed November 8, 2010, the contents of which are hereby incorporated by reference.

FIELD OF THE INVENTION

[0002] The invention provides tetrahydroquinoline and related compounds, methods of
5 inhibiting ROR γ activity and/or reducing the amount of IL-17 in a subject, and therapeutic uses of the tetrahydroquinoline and related compounds. In particular, the present invention provides 1-arylsulfonamide-tetrahydroquinoline and related compounds, methods of using such compounds to inhibit ROR γ activity and/or reduce the amount of IL-17 in a subject, and treat immune disorders and inflammatory disorders.

BACKGROUND OF THE INVENTION

10 [0003] Retinoid-related orphan receptors (ROR) are reported to have an important role in numerous biological processes. See, for example, Dussault *et al.* in *Mech. Dev.* (1998) vol. 70, 147–153; and Andre *et al.* in *EMBO J.* (1998) vol. 17, 3867–3877. Scientific investigations relating to each of retinoid-related orphan receptors ROR α , ROR β , and ROR γ have been described in the literature. See, for example, Hirose *et al.* in *Biochem. Biophys. Res. Commun.* (1994) vol. 205, 1976–1983; Giguere *et al.* in *Genes. Dev.* (1994) vol. 8, 538–553; Medvedev *et al.* in *Gene* (1996) vol. 181, 199–206; Ortiz *et al.* in *Mol. Endocrinol.* (1995) vol. 9, 1679–1691; Wiesenbergs *et al.* in *Nucleic Acids Res.* (1995) vol. 23, 327–333; Carlberg *et al.* in *Mol. Endocrinol.* (1994) vol. 8, 757–770; and Becker-Andre *et al.* in *Biochem. Biophys. Res. Commun.* (1993) vol. 194, 1371–1379. Continuing research in this field is spurred by the
15
20 promise of developing new therapeutic agents to treat medical disorders associated with retinoid-related orphan receptor activity.

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[0004] ROR γ has been reported to be expressed in high concentration in various tissues, such as thymus, kidney, liver, muscle, and certain fat tissue. See, for example, Hirose *et al.* in *Biochem. Biophys. Res. Commun.* (1994) vol. 205, 1976–1983; Medvedev *et al.* in *Gene* (1996) vol. 181, 199–206; Ortiz *et al.* in *Mol. Endocrinol.* (1995) vol. 9, 1679–1691; and He *et al.* in
5 *Immunity* (1998) vol. 9, 797–806. Two isoforms of ROR γ have been identified and are referred to as γ 1 and γ 2 (also referred to as ROR γ t). See, for example, He *et al.* in *Immunity* (1998) vol. 9, 797–806. Expression of the γ 2 isoform has been reported to appear in, for example, double-positive thymocytes. See, for example, He *et al.* in *Immunity* (1998) vol. 9, 797–806; and
10 Villey *et al.* in *Eur. J. Immunol.* (1999) vol. 29, 4072–4080. Compounds capable of modulating ROR γ t activity are contemplated to provide a therapeutic benefit in the treatment of multiple medical disorders, including immune and inflammatory disorders.

[0005] Numerous immune and inflammatory disorders continue to afflict millions of patients worldwide. Significant advances have been made in treating these disorders. However, current therapies do not provide satisfactory results for all patients due to, for
15 example, detrimental side effects or insufficient efficacy. Treatments for immune and inflammatory disorders vary depending on the particular medical disorder, and often involve use of immunosuppressive drugs. Surgery (*e.g.*, splenectomy), plasmapheresis, or radiation can be used in certain instances.

[0006] One exemplary immune disorder in need of better therapy is psoriasis. Psoriasis is a
20 T cell-mediated inflammatory disease that affects approximately 2% to 3% of adults and has a substantial adverse impact on the quality of life for patients suffering from this disorder. Plaques resulting from psoriasis can be painful and are visually unappealing. Various therapeutics have been developed in an attempt to treat psoriasis. However, the traditional therapies for psoriasis often have toxic adverse effects.

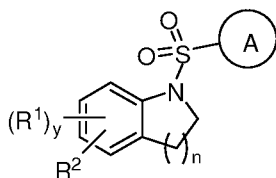
[0007] An exemplary inflammatory disorder in need of better treatment is rheumatoid
25 arthritis. This form of arthritis is characterized by inflammation in the synovial membrane and results in destruction of bone. Numerous therapeutics have been developed in an attempt to treat this disorder. Exemplary therapeutics for treating rheumatoid arthritis include corticosteroids, methotrexate, hydroxychloroquine, sulfasalazine, and leflunomide. However,
30 current therapies are not effective for all patients. Moreover, some patients develop resistance to current therapies.

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[0008] Accordingly, a need exists for improved treatments for immune disorders and inflammatory disorders. The present invention addresses this need and provides other related advantages.

SUMMARY

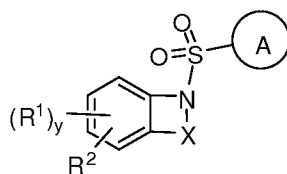
[0009] The present invention provides tetrahydroquinoline and related compounds, pharmaceutical compositions, methods of inhibiting ROR γ activity and/or reducing the amount of IL-17 in a subject, and methods of treating various medical disorders using such compounds. In particular, one aspect of the invention provides a collection of tetrahydroquinoline and related compounds, such as a compound represented by Formula I:



10

(I)

or a pharmaceutically acceptable salt or solvate thereof; wherein the variables are as defined in the detailed description. Other illustrative aspects of the invention provide a collection of tetrahydroquinoline and related compounds, such as a compound represented by Formula III:



15

(III)

or a pharmaceutically acceptable salt or solvate thereof; wherein the variables are as defined in the detailed description. Further description of additional collections of tetrahydroquinoline and related compounds are described in the detailed description.

[0010] Another aspect of the invention provides a method of treating a subject suffering from a medical disorder. The method comprises administering to the subject a therapeutically effective amount of one or more tetrahydroquinoline or related compounds described herein, e.g., a compound of Formula I, II, III, IV, V, VI, VII, VIII, or IX, wherein Formulae I-IX are as described in the detailed description. A large number of disorders can be treated using the

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tetrahydroquinoline and related compounds described herein. For example, the compounds described herein can be used to treat an immune disorder or inflammatory disorder, such as rheumatoid arthritis, psoriasis, chronic graft-versus-host disease, acute graft-versus-host disease, Crohn's disease, inflammatory bowel disease, multiple sclerosis, systemic lupus erythematosus, Celiac Sprue, idiopathic thrombocytopenic thrombotic purpura, myasthenia
5 gravis, Sjogren's syndrome, scleroderma, ulcerative colitis, asthma, epidermal hyperplasia, and other medical disorders described herein. In certain other embodiments, the disorder is rheumatoid arthritis.

[0011] Another aspect of the invention provides a method of inhibiting the activity of
10 ROR γ . The method comprises exposing a ROR γ to an effective amount of one or more tetrahydroquinoline or related compounds described herein, e.g., a compound of Formula I, II, III, IV, V, VI, VII, VIII, or IX, or a pharmaceutical composition described herein.

[0012] Another aspect of the invention provides a method of reducing the amount of IL-17
15 in a subject. The method comprises administering to a subject an effective amount of one or more tetrahydroquinoline or related compounds described herein, e.g., a compound of Formula I, II, III, IV, V, VI, VII, VIII, or IX, or a pharmaceutical composition described herein, to reduce the amount of IL-17 in the subject.

DETAILED DESCRIPTION OF THE INVENTION

[0013] The invention provides tetrahydroquinoline and related compounds, pharmaceutical compositions, methods of inhibiting ROR γ activity and/or reducing the amount of IL-17 in a
20 subject, and therapeutic uses of the tetrahydroquinoline and related compounds. The practice of the present invention employs, unless otherwise indicated, conventional techniques of organic chemistry, pharmacology, molecular biology (including recombinant techniques), cell biology, biochemistry, and immunology. Such techniques are explained in the literature, such as in "Comprehensive Organic Synthesis" (B.M. Trost & I. Fleming, eds., 1991-1992);
25 "Handbook of experimental immunology" (D.M. Weir & C.C. Blackwell, eds.); "Current protocols in molecular biology" (F.M. Ausubel *et al.*, eds., 1987, and periodic updates); and "Current protocols in immunology" (J.E. Coligan *et al.*, eds., 1991), each of which is herein incorporated by reference in its entirety.

[0014] Various aspects of the invention are set forth below in sections; however, aspects of
30 the invention described in one particular section are not to be limited to any particular section.

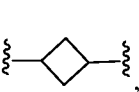
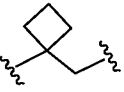
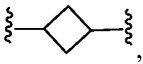
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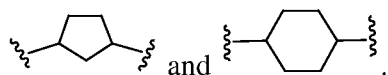
Further, when a variable is not accompanied by a definition, the previous definition of the variable controls.

Definitions

[0015] The terms used herein have their ordinary meaning and the meaning of such terms is independent at each occurrence thereof. That notwithstanding and except where stated otherwise, the following definitions apply throughout the specification and claims. Chemical names, common names, and chemical structures may be used interchangeably to describe the same structure. If a chemical compound is referred to using both a chemical structure and a chemical name, and an ambiguity exists between the structure and the name, the structure predominates. These definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated. Hence, the definition of "alkyl" applies to "alkyl" as well as the "alkyl" portions of "hydroxyalkyl," "fluoroalkyl," "-O-alkyl," etc.

[0016] The term "alkyl" is art-recognized, and includes saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In certain embodiments, a straight chain or branched chain alkyl has about 30 or fewer carbon atoms in its backbone (e.g., C₁-C₃₀ for straight chain, C₃-C₃₀ for branched chain), and alternatively, about 20 or fewer. Likewise, cycloalkyls have from about 3 to about 10 carbon atoms in their ring structure, and alternatively about 5, 6 or 7 carbons in the ring structure. Exemplary alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, cyclopropyl, and cyclobutyl.

[0017] The term "alkylene" refers to a diradical of an alkyl group. Exemplary alkylene groups include -CH₂CH₂-, , and . The term "cycloalkylene" refers to a diradical of a cycloalkyl group. Exemplary cycloalkylene groups include ,

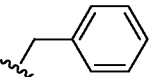
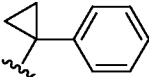


[0018] The term "haloalkyl" refers to an alkyl group that is substituted with at least one halogen. Exemplary haloalkyl groups include -CH₂F, -CHF₂, -CF₃, -CH₂CF₃, -CF₂CF₃, and the like.

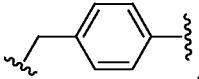
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[0019] The term "hydroxyalkyl" refers to an alkyl group that is substituted with at least one hydroxyl group. Exemplary hydroxyl alkyl groups include $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{C}(\text{H})(\text{OH})\text{C}(\text{OH})\text{H}_2$, and the like.

[0020] The term "aralkyl" refers to an alkyl group substituted with an aryl group.

5 Exemplary aralkyl groups include  and .

[0021] The term "aralkylene" refers to a diradical of an aralkyl group. An exemplary

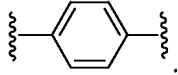
aralkylene group is .

[0022] The term "heteroaralkyl" refers to an alkyl group substituted with a heteroaryl group.

10 **[0023]** The terms "alkenyl" and "alkynyl" are art-recognized and refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

[0024] The term "aryl" is art-recognized and refers to a carbocyclic aromatic group. Representative aryl groups include phenyl, naphthyl, anthracenyl, and the like. Unless
15 specified otherwise, the aromatic ring may be substituted at one or more ring positions with, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, nitro, sulfhydryl, imino, amido, carboxylic acid, $-\text{C}(\text{O})\text{alkyl}$, $-\text{CO}_2\text{alkyl}$, carbonyl, carboxyl, alkylthio, sulfonyl, sulfonamido, sulfonamide, ketone, aldehyde, ester, heterocyclyl, aryl or heteroaryl moieties, $-\text{CF}_3$, $-\text{CN}$, or the like. The term "aryl" also includes polycyclic aromatic
20 ring systems having two or more carbocyclic rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein all of the fused rings are aromatic rings, e.g., in a naphthyl group.

[0025] The term "arylene" as used herein refers to a divalent radical of a carbocyclic aromatic group. Arylene may be optionally substituted as described for aryl, or as otherwise

25 indicated. An exemplary arylene group is .

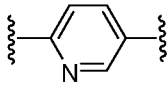
[0026] The term "heteroaryl" is art-recognized and refers to aromatic groups that include at least one ring heteroatom. In certain instances, a heteroaryl group contains 1, 2, 3, or 4 ring heteroatoms. Representative examples of heteroaryl groups include pyrrolyl, furanyl,

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thiophenyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyrazolyl, pyridinyl, pyrazinyl, pyridazinyl and pyrimidinyl, and the like. Unless specified otherwise, the heteroaryl ring may be substituted at one or more ring positions with, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, nitro, sulfhydryl, imino, amido, carboxylic acid, -C(O)alkyl, -CO₂alkyl, carbonyl, carboxyl, alkylthio, sulfonyl, sulfonamido, sulfonamide, ketone, aldehyde, ester, heterocyclyl, aryl or heteroaryl moieties, -CF₃, -CN, or the like. The term "heteroaryl" also includes polycyclic aromatic ring systems having two or more rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein all of the fused rings are heteroaromatic, e.g., in a naphthyridinyl group.

10 **[0027]** The terms ortho, meta and para are art-recognized and refer to 1,2-, 1,3- and 1,4-disubstituted benzenes, respectively. For example, the names 1,2-dimethylbenzene and ortho-dimethylbenzene are synonymous.

[0028] The term "heteroarylene" as used herein refers to a divalent radical of aromatic groups that include at least one ring heteroatom, for example, one to four heteroatoms, such as nitrogen, oxygen, and sulfur. Heteroarylene may be optionally substituted as described for

15 heteroaryl, or as otherwise indicated. An exemplary heteroarylene group is .

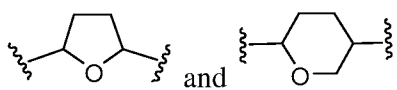
[0029] As used herein, the terms "heterocyclic" and "heterocyclyl" represent, for example, an aromatic or nonaromatic ring (e.g., a monocyclic or bicyclic ring) containing one or more heteroatoms. The heteroatoms can be the same or different from each other. Examples of heteroatoms include, but are not limited to nitrogen, oxygen and sulfur. Aromatic and nonaromatic heterocyclic rings are well-known in the art. Some nonlimiting examples of aromatic heterocyclic rings include, but not limited to, pyridine, pyrimidine, indole, purine, quinoline and isoquinoline. Nonlimiting examples of nonaromatic heterocyclic compounds include, but not limited to, piperidine, piperazine, morpholine, pyrrolidine and pyrazolidine. Examples of oxygen containing heterocyclic rings include, but not limited to, furan, oxirane, 2H-pyran, 4H-pyran, 2H-chromene, benzofuran, and 2,3-dihydrobenzo[b][1,4]dioxine. Examples of sulfur-containing heterocyclic rings include, but are not limited to, thiophene, benzothiophene, and parathiazine. Examples of nitrogen containing rings include, but not limited to, pyrrole, pyrrolidine, pyrazole, pyrazolidine, imidazole, imidazoline, imidazolidine, pyridine, piperidine, pyrazine, piperazine, pyrimidine, indole, purine, benzimidazole, quinoline, isoquinoline, triazole, and triazine. Examples of heterocyclic rings containing two different

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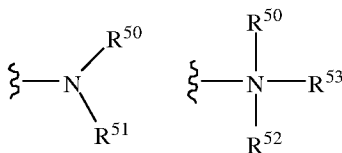
heteroatoms include, but are not limited to, phenothiazine, morpholine, parathiazine, oxazine, oxazole, thiazine, and thiazole. The heterocyclic ring is optionally further substituted at one or more ring positions with, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, nitro, sulfhydryl, imino, amido, carboxylic acid, -
 5 C(O)alkyl, -CO₂alkyl, carbonyl, carboxyl, alkylthio, sulfonyl, sulfonamido, sulfonamide, ketone, aldehyde, ester, heterocyclyl, aryl or heteroaryl moieties, -CF₃, -CN, or the like. In certain embodiments, the heterocyclyl group is a 3-7 membered ring that, unless specified otherwise, is substituted or unsubstituted.

[0030] The term “heterocycloalkyl” refers to a saturated heterocyclyl group having, for
 10 example, 3-7 ring atoms.

[0031] The term “heterocycloalkylene” refers to a diradical of a heterocycloalkyl group.

Exemplary heterocycloalkylene groups include  and .

[0032] The terms “amine” and “amino” are art-recognized and refer to both unsubstituted and substituted amines, e.g., a moiety that may be represented by the general formulas:



15

wherein R⁵⁰, R⁵¹, R⁵² and R⁵³ each independently represent a hydrogen, an alkyl, an alkenyl, -(CH₂)_m-R⁶¹, or R⁵⁰ and R⁵¹, taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure; R⁶¹ represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle or a polycycle; and m is zero or an integer in the range
 20 of 1 to 8. In certain embodiments, only one of R⁵⁰ or R⁵¹ may be a carbonyl, e.g., R⁵⁰, R⁵¹ and the nitrogen together do not form an imide. In other embodiments, R⁵⁰ and R⁵¹ (and optionally R⁵²) each independently represent a hydrogen, an alkyl, an alkenyl, or -(CH₂)_m-R⁶¹.

[0033] The terms “alkoxy” or “alkoxy” are art-recognized and refer to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxy groups
 25 include methoxy, ethoxy, propoxy, tert-butoxy and the like. An “ether” is two hydrocarbons covalently linked by an oxygen. Accordingly, the substituent of an alkyl that renders that alkyl an ether is or resembles an alkoxy, such as may be represented by one of -O-alkyl, -O-alkenyl, -O-alkynyl, and -O-(CH₂)_m-R⁶¹, where m and R⁶¹ are described above.

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[0034] The symbol “~” indicates a point of attachment.

[0035] The term “substituted” means that one or more hydrogens on the atoms of the designated group are replaced with a selection from the indicated group, provided that the atoms’ normal valencies under the existing circumstances are not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. The terms “stable compound” or “stable structure” refer to a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

10 [0036] When any substituent or variable occurs more than one time in any constituent or the compound of the invention, its definition on each occurrence is independent of its definition at every other occurrence, unless otherwise indicated.

[0037] The location of a substituent on the tetrahydroquinoline or benzoxazine core can be characterized according to positional numbering in accordance with the rules of chemical nomenclature. Positional numbering for the tetrahydroquinoline and benzoxazine cores is illustrated below.



[0038] It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

[0039] One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-

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limiting examples of suitable solvates include ethanlates, methanlates, and the like.

"Hydrate" is a solvate wherein the solvent molecule is H₂O.

[0040] Certain compounds contained in compositions of the present invention may exist in particular geometric or stereoisomeric forms. Further, certain compounds described herein
5 may be optically active. The present invention contemplates all such compounds, including cis- and trans-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. The compounds may contain one or more stereogenic centers. For example, asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such
10 isomers, as well as mixtures thereof, are intended to be included in this invention, such as, for example, racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers, and it is intended that all of the possible optical isomers, diastereomers in
15 mixtures, and pure or partially purified compounds are included within the ambit of this invention.

[0041] Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be
20 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 alcohol or Mosher's acid chloride), separating the diastereomers and converting (*e.g.*, hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Alternatively, a particular enantiomer of a compound of the present invention may be prepared by asymmetric synthesis.
25 Still further, where the molecule contains a basic functional group (such as amino) or an acidic functional group (such as carboxylic acid) diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means known in the art, and subsequent recovery of the pure enantiomers.

[0042] Individual stereoisomers of the compounds of the invention may, for example, be
30 substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. Chiral center(s) in a compound of the present invention

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can have the *S* or *R* configuration as defined by the *IUPAC* 1974 Recommendations. Further, to the extent a compound described herein may exist as a atropisomer (*e.g.*, substituted biaryls), all forms of such atropisomer are considered part of this invention.

5 [0043] As used herein, the terms “subject” and “patient” are used interchangeable and refer to organisms to be treated by the methods of the present invention. Such organisms preferably include, but are not limited to, mammals (*e.g.*, murines, simians, equines, bovines, porcines, canines, felines, and the like), and most preferably includes humans.

[0044] The term "IC₅₀" is art-recognized and refers to the concentration of a compound that is required for 50% inhibition of its target.

10 [0045] As used herein, the term “effective amount” refers to the amount of a compound sufficient to effect beneficial or desired results (*e.g.*, a therapeutic, ameliorative, inhibitory or preventative result). An effective amount can be administered in one or more administrations, applications or dosages and is not intended to be limited to a particular formulation or administration route. As used herein, the term “treating” includes any effect, *e.g.*, lessening, 15 reducing, modulating, ameliorating or eliminating, that results in the improvement of the condition, disease, disorder, and the like, or ameliorating a symptom thereof.

[0046] As used herein, the term “pharmaceutical composition” refers to the combination of an active agent with a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use *in vivo* or *ex vivo*.

20 [0047] As used herein, the term “pharmaceutically acceptable carrier” refers to any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water, emulsions (*e.g.*, such as an oil/water or water/oil emulsions), and various types of wetting agents. The compositions also can include stabilizers and preservatives. For examples of carriers, stabilizers and adjuvants. (*See e.g.*, Martin, Remington's Pharmaceutical Sciences, 15th Ed., 25 Mack Publ. Co., Easton, PA [1975]).

[0048] As used herein, the term “pharmaceutically acceptable salt” refers to any pharmaceutically acceptable salt (*e.g.*, acid or base) of a compound of the present invention which, upon administration to a subject, is capable of providing a compound of this invention or an active metabolite or residue thereof. As is known to those of skill in the art, “salts” of the 30 compounds of the present invention may be derived from inorganic or organic acids and bases. Examples of acids include, but are not limited to, hydrochloric, hydrobromic, sulfuric, nitric,

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perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic, benzenesulfonic acid, and the like. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

[0049] Examples of bases include, but are not limited to, alkali metals (*e.g.*, sodium) hydroxides, alkaline earth metals (*e.g.*, magnesium), hydroxides, ammonia, and compounds of formula NW_4^+ , wherein W is C_{1-4} alkyl, and the like.

[0050] Examples of salts include, but are not limited to: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, flucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate (also known as toluenesulfonate), undecanoate, and the like. Other examples of salts include anions of the compounds of the present invention compounded with a suitable cation such as Na^+ , NH_4^+ , and NW_4^+ (wherein W is a C_{1-4} alkyl group), and the like. Further examples of salts include, but are not limited to: ascorbate, borate, nitrate, phosphate, salicylate, and sulfate. Further, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al.*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use*. (2002) Zurich: Wiley-VCH; S. Berge *et al.*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al.*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference.

[0051] Additional exemplary basic salts include, but are not limited to: ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the

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like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (*e.g.*, methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (*e.g.*, dimethyl, diethyl, and dibutyl sulfates), long chain halides (*e.g.*, decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (*e.g.*, benzyl and phenethyl bromides), and
5 others.

[0052] For therapeutic use, salts of the compounds of the present invention are contemplated as being pharmaceutically acceptable. However, salts of acids and bases that are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

10 **[0053]** In addition, when a compound of the invention contains both a basic moiety (such as, but not limited to, a pyridine or imidazole) and an acidic moiety (such as, but not limited to, a carboxylic acid) zwitterions ("inner salts") may be formed. Such acidic and basic salts used within the scope of the invention are pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable) salts. Such salts of the compounds of the invention may be formed,
15 for example, by reacting a compound of the invention with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

[0054] The present invention includes the compounds of the invention in all their isolated forms (such as any solvates, hydrates, stereoisomers, and tautomers thereof). Further, the
20 invention include compounds in which one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of the invention. For example, different isotopic forms of hydrogen (H) include protium (¹H) and deuterium
25 (²H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds can be prepared without undue experimentation by conventional techniques known to those skilled in the art or by processes
30 analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

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[0055] The term “SEA Syndrome” refers to Seronegativity, Enthesopathy, Arthropathy Syndrome.

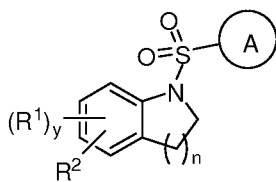
[0056] Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes and methods are described as having, including, or comprising specific steps, it is contemplated that, additionally, there are compositions of the present invention that consist essentially of, or consist of, the recited components, and that there are processes and methods according to the present invention that consist essentially of, or consist of, the recited processing steps.

[0057] The terms “a” and “an” as used herein mean “one or more” and include the plural unless the context is inappropriate

[0058] As a general matter, compositions specifying a percentage are by weight unless otherwise specified.

I. Tetrahydroquinoline and Related Compounds

[0059] One aspect of the invention provides a compound represented by Formula I:



15

(I)

or a pharmaceutically acceptable salt or solvate thereof; wherein:

A is aryl or aralkyl; each of which is substituted with 1, 2, or 3 substituents independently selected from the group consisting of C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, $-N(R^3)(R^4)$, hydroxyl, $-CO_2R^6$, $-C_{1-6}$ alkylene- $N(R^3)(R^4)$, $-C_{1-6}$ alkylene- C_{1-6} alkoxy, $-C_{1-6}$ alkylene- CO_2R^6 , $-O$ -aryl, $-O$ - C_{1-6} alkylene- $N(R^3)(R^4)$, $-O$ - C_{1-6} alkylene- CO_2R^6 , $-N(R^5)C(O)$ - C_{1-6} alkylene- $N(R^3)(R^4)$, $-CN$, $-S(O)_p$ - C_{1-6} alkyl, $-SO_2N(R^3)(R^4)$, $-N(R^3)SO_2$ (C_{1-6} alkyl), heterocyclyl, $-C(O)$ - C_{1-6} alkyl, $-C(O)N(R^3)(R^4)$, and $-N(R^3)C(O)N(R^3)(R^4)$;

R^1 represents independently for each occurrence hydrogen, halogen, or C_{1-6} alkyl;

R^2 is $-N(R^7)C(O)R^8$, $-(C_{1-2}alkylene)-N(R^7)C(O)R^8$, $-N(R^7)C(O)N(R^7)(R^8)$, or heteroaryl, wherein said heteroaryl group is optionally substituted with 1 or 2 substituents independently

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selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, heteroaryl, and -N(R³)(R⁴);

R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclic ring;

R⁵ represents independently for each occurrence hydrogen or C₁₋₆alkyl;

R⁶ and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;

R⁸ is aryl, aralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -C(R⁶)₂-cycloalkyl, -C(R⁶)₂-cycloalkenyl, -C(R⁶)₂-heterocyclyl, or C₁₋₆alkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, -C(O)N(R³)(R⁴), -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

n is 1 or 2;

p represents independently for each occurrence 0, 1, or 2;

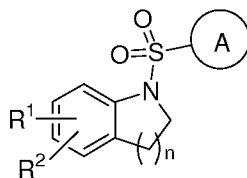
y is 1 or 2; and

wherein the stereochemical configuration at a stereocenter in a compound represented by Formula I is *R*, *S*, or a mixture thereof.

[0060] In certain embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of C₁₋₆haloalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R⁵)C(O)-C₁₋₆alkylene-N(R³)(R⁴). In certain embodiments, R² is -N(R⁷)C(O)R⁸. In certain embodiments, R⁸ is aryl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl. In certain embodiments, R⁸ is phenyl substituted with 2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl, where the first substituent is located at the 2-position of the phenyl group, and the second substituent is located at the 6-position of the phenyl group. In certain embodiments, y is 1.

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[0061] Another aspect of the invention provides a compound represented by Formula I-A:



(I-A)

or a pharmaceutically acceptable salt or solvate thereof; wherein:

- 5 A is aryl or aralkyl; each of which is substituted with 1, 2, or 3 substituents independently selected from the group consisting of C₁₋₆haloalkyl, -N(R³)(R⁴), hydroxyl, -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), -O-C₁₋₆alkylene-CO₂R⁶, -N(R⁵)C(O)-C₁₋₆alkylene-N(R³)(R⁴), -CN, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);
- 10 R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;
 R² is -N(R⁷)C(O)R⁸, -(C₁₋₂alkylene)-N(R⁷)C(O)R⁸, or heteroaryl, wherein said heteroaryl group is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, heteroaryl, and -N(R³)(R⁴);
- 15 R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclic ring;
 R⁵ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;
 R⁶ and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;
- 20 R⁸ is aryl, aralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -C(R⁶)₂-cycloalkyl, -C(R⁶)₂-cycloalkenyl, -C(R⁶)₂-heterocyclyl, or C₁₋₆alkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);
- 25 n is 1 or 2;
 p represents independently for each occurrence 0, 1, or 2; and

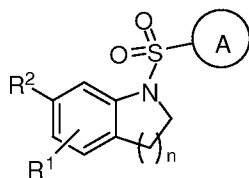
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wherein the stereochemical configuration at a stereocenter in a compound represented by Formula I-A is *R*, *S*, or a mixture thereof.

[0062] In certain embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of C₁₋₆haloalkyl, -N(R³)(R⁴), hydroxyl, -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R⁵)C(O)-C₁₋₆alkylene-N(R³)(R⁴). In certain embodiments, n is 2. In certain embodiments, n is 2, and R² is attached to the 7-position of the tetrahydroquinoline ring. In certain embodiments, R² is -N(R⁷)C(O)R⁸. In certain embodiments, R⁸ is aryl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, and -S-C₁₋₆alkyl. In certain embodiments, R⁸ is phenyl substituted with 2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl, where the first substituent is located at the 2-position of the phenyl group, and the second substituent is located at the 6-position of the phenyl group.

15

[0063] Another aspect of the invention provides a compound represented by Formula I-B:



(I-B)

or a pharmaceutically acceptable salt or solvate thereof; wherein:

20 A is aryl or aralkyl; each of which is substituted with 1, 2, or 3 substituents independently selected from the group consisting of C₁₋₆haloalkyl, -N(R³)(R⁴), hydroxyl, -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), -O-C₁₋₆alkylene-CO₂R⁶, -N(R⁵)C(O)-C₁₋₆alkylene-N(R³)(R⁴), -CN, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

25 R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

R² is -N(R⁷)C(O)R⁸, -(C₁₋₂alkylene)-N(R⁷)C(O)R⁸, or heteroaryl, wherein said heteroaryl group is optionally substituted with 1 or 2 substituents independently selected from

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the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, heteroaryl, and -N(R³)(R⁴);

R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclic ring;

R⁵ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

R⁶ and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;

R⁸ is aryl, aralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -C(R⁶)₂-cycloalkyl, -C(R⁶)₂-cycloalkenyl, -C(R⁶)₂-heterocyclyl, or C₁₋₆alkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

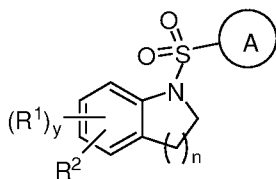
n is 1 or 2;

p represents independently for each occurrence 0, 1, or 2; and

wherein the stereochemical configuration at a stereocenter in a compound represented by Formula I-B is *R*, *S*, or a mixture thereof.

[0064] In certain embodiments, variables A, R¹ through R⁸, n, and p for Formula I-B are as defined by one of the further embodiments specified above in connection with Formula I-A.

[0065] Another aspect of the invention provides a compound of Formula II:



(II)

or a pharmaceutically acceptable salt or solvate thereof; wherein:

A is cycloalkyl, heterocycloalkyl, or heteroaryl containing at least one ring nitrogen or ring oxygen atom; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋

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₆hydroxyalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-aryl, -O-C₁₋₆alkylene-N(R³)(R⁴), -N(R⁵)C(O)-C₁₋₆alkylene-N(R³)(R⁴), -CN, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), -N(R³)SO₂(C₁₋₆alkyl), heterocyclyl, -C(O)-C₁₋₆alkyl, -C(O)N(R³)(R⁴), and -N(R³)C(O)N(R³)(R⁴);

5 R¹ represents independently for each occurrence hydrogen or C₁₋₆alkyl;

R² is -N(R⁷)C(O)R⁸, -(C₁₋₂alkylene)-N(R⁷)C(O)R⁸, -N(R⁷)C(O)N(R⁷)(R⁸), or heteroaryl, wherein said heteroaryl group is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, heteroaryl, and -N(R³)(R⁴);

10 R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclic ring;

R⁵ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

R⁶ and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;

15 R⁸ is aryl, aralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -C(R⁶)₂-cycloalkyl, -C(R⁶)₂-cycloalkenyl, -C(R⁶)₂-heterocyclyl, or C₁₋₆alkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, -C(O)N(R³)(R⁴), -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

20 n is 1 or 2;

p represents independently for each occurrence 0, 1, or 2;

y is 1 or 2; and

wherein the stereochemical configuration at a stereocenter in a compound represented by Formula II is *R*, *S*, or a mixture thereof.

25 **[0066]** In certain embodiments, n is 2, and R² is attached at the 7-position of the tetrahydroquinoline ring.

[0067] In certain embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl,

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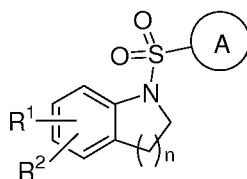
-N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴).

[0068] In certain embodiments, R² is -N(R⁷)C(O)R⁸.

[0069] In certain embodiments, R⁸ is aryl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl. In certain embodiments, R⁸ is phenyl substituted with 2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl, where the first substituent is located at the 2-position of the phenyl group, and the second substituent is located at the 6-position of the phenyl group. In certain embodiments, y is 1.

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[0070] Another aspect of the invention provides a compound of Formula II-A:



(II-A)

or a pharmaceutically acceptable salt or solvate thereof; wherein:

15 A is cycloalkyl, heterocycloalkyl, or heteroaryl containing at least one ring nitrogen or ring oxygen atom; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), -N(R⁵)C(O)-C₁₋₆alkylene-N(R³)(R⁴), -CN, -S(O)_pC₁₋₆alkyl, **20** -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

R² is -N(R⁷)C(O)R⁸, -(C₁₋₂alkylene)-N(R⁷)C(O)R⁸, or heteroaryl, wherein said heteroaryl group is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, heteroaryl, **25** and -N(R³)(R⁴);

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R^3 and R^4 each represent independently hydrogen or C_{1-6} alkyl; or R^3 and R^4 taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclic ring;

R^5 represents independently for each occurrence hydrogen, halogen, or C_{1-6} alkyl;

5 R^6 and R^7 each represent independently for each occurrence hydrogen or C_{1-6} alkyl;

R^8 is aryl, aralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, $-C(R^6)_2$ -cycloalkyl, $-C(R^6)_2$ -cycloalkenyl, $-C(R^6)_2$ -heterocyclyl, or C_{1-6} alkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, $-N(R^3)(R^4)$, $-CN$, $-CO_2-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkyl, $-S(O)_pC_{1-6}$ alkyl, $-SO_2N(R^3)(R^4)$, and $-N(R^3)SO_2(C_{1-6}alkyl)$;

n is 1 or 2;

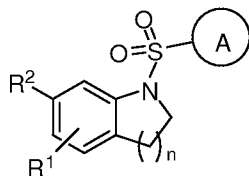
p represents independently for each occurrence 0, 1, or 2; and

wherein the stereochemical configuration at a stereocenter in a compound represented by Formula II-A is *R*, *S*, or a mixture thereof.

15 **[0071]** In certain embodiments, A is heteroaryl containing at least one ring nitrogen or ring oxygen atom; wherein said heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-N(R^3)(R^4)$, $-CO_2R^6$, $-C_{1-6}alkylene-N(R^3)(R^4)$, $-C_{1-6}alkylene-C_{1-6}alkoxy$, $-C_{1-6}alkylene-CO_2R^6$, $-O-C_{1-6}alkylene-N(R^3)(R^4)$, and $-N(R^5)C(O)-C_{1-6}alkylene-N(R^3)(R^4)$. In certain embodiments, 20 R^1 is hydrogen. In certain embodiments, R^2 is $-N(R^7)C(O)R^8$. In certain embodiments, n is 2. In certain embodiments, n is 2, and R^2 is attached to the 7-position of the tetrahydroquinoline ring. In certain embodiments, R^8 is phenyl substituted with 2 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, and C_{1-6} haloalkyl, where the first substituent is located at the 2-position of the phenyl group, and the second substituent is located 25 at the 6-position of the phenyl group.

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[0072] Another aspect of the invention provides a compound of Formula II-B:



(II-B)

or a pharmaceutically acceptable salt or solvate thereof; wherein:

- 5 A is cycloalkyl, heterocycloalkyl, or heteroaryl containing at least one ring nitrogen or ring oxygen atom; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), -N(R⁵)C(O)-C₁₋₆alkylene-N(R³)(R⁴), -CN, -S(O)_pC₁₋₆alkyl,
- 10 -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

- R² is -N(R⁷)C(O)R⁸, -(C₁₋₂alkylene)-N(R⁷)C(O)R⁸, or heteroaryl, wherein said heteroaryl group is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, heteroaryl,
- 15 and -N(R³)(R⁴);

R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclic ring;

R⁵ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

- 20 R⁶ and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;

- R⁸ is aryl, alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -C(R⁶)₂-cycloalkyl, -C(R⁶)₂-cycloalkenyl, -C(R⁶)₂-heterocyclyl, or C₁₋₆alkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);
- 25

n is 1 or 2;

p represents independently for each occurrence 0, 1, or 2; and

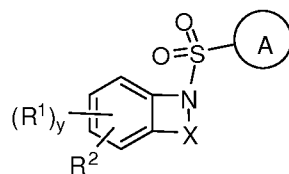
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wherein the stereochemical configuration at a stereocenter in a compound represented by Formula II-B is *R*, *S*, or a mixture thereof

[0073] In certain embodiments, variables A, R¹ through R⁸, n, and p for Formula II-B are as defined by one of the further embodiments specified above in connection with Formula II-A.

5

[0074] Another aspect of the invention provides a compound of Formula III:



(III)

or a pharmaceutically acceptable salt or solvate thereof; wherein:

10 A is aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-aryl, -O-C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-CO₂R⁶, -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴), -CN, 15 -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), -N(R³)SO₂(C₁₋₆alkyl), heterocyclyl, C(O)R¹¹, -C(R¹¹)(R¹²)OH, -C(O)N(R³)(R⁴), and -N(R³)C(O)N(R³)(R⁴);

X is -O-[C(R⁶)₂]_m-ψ, -O-[C(R⁶)(R⁹)C(R⁶)₂]-ψ, -O-[C(R⁶)(R⁹)]-ψ, -O-[C(R⁶)₂-C(hydroxyC₁₋₆alkyl)(R⁶)]-ψ, -C(R⁵)(C₁₋₆alkyl)[C(R⁵)₂]_m-ψ, -[C(R⁵)₂]_m-C(R⁵)(C₁₋₆alkyl)-ψ, -C(R⁵)₂-C(R⁵)(C₁₋₆alkyl)-C(R⁵)₂-ψ, -C(R⁵)₂C(R⁶)=C(R⁶)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, 20 -C(R⁶)=C(R⁶)-ψ, -N(R⁶)-[C(R⁶)₂]_m-ψ, -N=C(R⁶)-ψ, -N=C(R⁶)C(R⁶)₂-ψ, -N=N-ψ, -C(R⁶)=N-ψ, -C(R¹⁰)=N-ψ, -C(R⁶)₂C(O)C(R⁶)₂-ψ, -[C(R⁶)₂]_m-C(O)-ψ, -C(R⁶)=C(R⁶)C(O)-ψ, -C(O)C(R⁶)=C(R⁶)-ψ, -N(R⁶)-C(O)-ψ, or -C(H)(OR⁶)-[C(R⁶)₂]_m-ψ; wherein ψ is a bond to the sulfonamide ring nitrogen atom in Formula III;

R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

25 R² is -N(R⁷)C(O)R⁸, -(C₁₋₂alkylene)-N(R⁷)C(O)R⁸, -N(R⁷)C(O)N(R⁷)(R⁸), or heteroaryl, wherein said heteroaryl group is optionally substituted with 1 or 2 substituents independently

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selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, heteroaryl, and -N(R³)(R⁴);

R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclic ring;

R⁵ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

R⁶ and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;

R⁸ is aryl, aralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -C(R⁶)₂-cycloalkyl, -C(R⁶)₂-cycloalkenyl, -C(R⁶)₂-heterocyclyl, or C₁₋₆alkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, -C(O)N(R³)(R⁴), -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

R⁹ and R¹⁰ each represent independently C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-N(R³)C(O)-C₁₋₆alkyl, -C₁₋₆alkylene-CO₂R³, -C₁₋₆alkylene-CN, -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-C(O)N(R³)(R⁴), -C(O)N(R³)(R⁴), -C₁₋₆alkylene-N(R³)C(O)N(R³)(R⁴), -C₁₋₆alkylene-N(R³)C(O)-[C(OH)(R³)(R⁴)], -C₁₋₆alkylene-O-C(O)N(R³)(R⁴), -C₁₋₆alkylene-SO₂N(R³)(R⁴), -C₁₋₆alkylene-N(R³)SO₂N(R³)(R⁴), C₂₋₄alkenyl, -arylene-CO₂R⁶, or -CN;

R¹¹ is C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl; each of which is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, hydroxyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, -CO₂R³, and, -N(R³)(R⁴);

R¹² is hydrogen, C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl; each of which is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, hydroxyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, -CO₂R³, and, -N(R³)(R⁴);

m is 1 or 2;

p represents independently for each occurrence 0, 1, or 2;

y is 1 or 2; and

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wherein the stereochemical configuration at a stereocenter in a compound represented by Formula III is *R*, *S*, or a mixture thereof.

[0075] In certain embodiments, A is aryl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂R⁶, -C(O)-C₁₋₆alkyl, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴). In certain other embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂R⁶, -C(O)-C₁₋₆alkyl, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴). In yet other embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, and -CN.

[0076] In certain embodiments, X is -O-[C(R⁶)₂]_m-ψ or -O-[C(R⁶)(R⁹)C(R⁶)₂]-ψ. In certain other embodiments, X is -C(R⁶)=N-ψ or -C(R¹⁰)=N-ψ. In yet other embodiments, X is -C(R⁵)(C₁₋₆alkyl)[C(R⁵)₂]_m-ψ, -[C(R⁵)₂]_m-C(R⁵)(C₁₋₆alkyl)-ψ, -C(R⁵)₂-C(R⁵)(C₁₋₆alkyl)-C(R⁵)₂-ψ, -C(R⁵)₂C(R⁶)=C(R⁶)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, or -C(R⁶)=C(R⁶)-ψ.

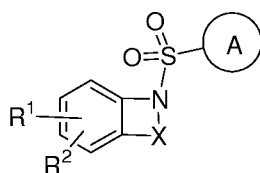
[0077] In certain embodiments, R² is -N(R⁷)C(O)R⁸.

[0078] In certain embodiments, R⁸ is aryl or aralkyl, each of which is substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl. In certain other embodiments, R⁸ is aryl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl. In certain other embodiments, R⁸ is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl. In certain other embodiments, R⁸ is phenyl substituted with 2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl, where the first substituent is located at the 2-position of the phenyl group, and the second substituent is located at the 6-position of the phenyl group.

[0079] In certain embodiments, y is 1.

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[0080] Another aspect of the invention provides a compound of Formula III-A:



(III-A)

5 or a pharmaceutically acceptable salt or solvate thereof; wherein:

A is aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-CO₂R⁶, -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴), -CN, -

10 S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

X is -C(R⁵)(C₁₋₆alkyl)[C(R⁵)₂]_m-ψ, -[C(R⁵)₂]_m-C(R⁵)(C₁₋₆alkyl)-ψ, -C(R⁵)₂-C(R⁵)(C₁₋₆alkyl)-C(R⁵)₂-ψ, -C(R⁵)₂C(R⁶)=C(R⁸)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, -C(R⁶)=C(R⁶)-ψ, -O-[C(R⁶)₂]_m-ψ, -N(R⁶)-[C(R⁶)₂]_m-ψ, -N=C(R⁶)-ψ, -N=C(R⁶)C(R⁶)₂-ψ, -N=N-ψ, -C(R⁶)=N-ψ, -C(O)-[C(R⁶)₂]_m-ψ, -C(R⁶)₂C(O)C(R⁶)₂-ψ, -[C(R⁶)₂]_m-C(O)-ψ, -C(R⁶)=C(R⁶)C(O)-ψ, -C(O)C(R⁶)=C(R⁶)-ψ, -N(R⁶)-C(O)-ψ, or -C(H)(OR⁶)-[C(R⁶)₂]_m-ψ; wherein ψ is a bond to the sulfonamide ring nitrogen atom in Formula III-A;

R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

15 R² is -N(R⁷)C(O)R⁸, -(C₁₋₂alkylene)-N(R⁷)C(O)R⁸, or heteroaryl, wherein said heteroaryl group is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, heteroaryl, and -N(R³)(R⁴);

20 R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclic ring;

R⁵ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

R⁶ and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;

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R⁸ is aryl, aralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -C(R⁶)₂-cycloalkyl, -C(R⁶)₂-cycloalkenyl, -C(R⁶)₂-heterocyclyl, or C₁₋₆alkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

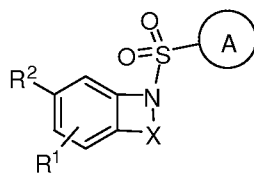
m is 1 or 2;

p represents independently for each occurrence 0, 1, or 2; and

wherein the stereochemical configuration at a stereocenter in a compound represented by Formula III-A is *R*, *S*, or a mixture thereof.

10 **[0081]** In certain embodiments, A is phenyl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴). In certain embodiments, X is -C(R⁵)(C₁₋₆alkyl)[C(R⁵)₂]_m-ψ, -[C(R⁵)₂]_m-C(R⁵)(C₁₋₆alkyl)-ψ, -C(R⁵)₂-C(R⁵)(C₁₋₆alkyl)-C(R⁵)₂-ψ, -C(R⁵)₂C(R⁶)=C(R⁸)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, or -C(R⁶)=C(R⁶)-ψ. In certain embodiments, X is -C(O)-[C(R⁶)₂]_m-ψ. In certain embodiments, R² is -N(R⁷)C(O)R⁸. In certain embodiments, R⁵ is hydrogen. In certain embodiments, R⁸ is aryl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, and -S-C₁₋₆alkyl. In certain embodiments, R⁸ is phenyl substituted with 2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl, where the first substituent is located at the 2-position of the phenyl group, and the second substituent is located at the 6-position of the phenyl group.

25 **[0082]** Another aspect of the invention provides a compound of Formula III-B:



(III-B)

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or a pharmaceutically acceptable salt or solvate thereof; wherein:

A is aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋

5 ₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋
₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-CO₂R⁶, -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴), -CN, -
 S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

X is -C(R⁵)(C₁₋₆alkyl)[C(R⁵)₂]_m-ψ, -[C(R⁵)₂]_m-C(R⁵)(C₁₋₆alkyl)-ψ, -C(R⁵)₂-C(R⁵)(C₁₋
 6alkyl)-C(R⁵)₂-ψ, -C(R⁵)₂C(R⁶)=C(R⁸)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, -C(R⁶)=C(R⁶)-ψ, -O-
 10 [C(R⁶)₂]_m-ψ, -N(R⁶)-[C(R⁶)₂]_m-ψ, -N=C(R⁶)-ψ, -N=C(R⁶)C(R⁶)₂-ψ, -N=N-ψ, -C(R⁶)=N-ψ,
 -C(O)-[C(R⁶)₂]_m-ψ, -C(R⁶)₂C(O)C(R⁶)₂-ψ, -[C(R⁶)₂]_m-C(O)-ψ, -C(R⁶)=C(R⁶)C(O)-ψ,
 -C(O)C(R⁶)=C(R⁶)-ψ, -N(R⁶)-C(O)-ψ, or -C(H)(OR⁶)-[C(R⁶)₂]_m-ψ; wherein ψ is a bond to the
 sulfonamide ring nitrogen atom in Formula III-B;

R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

15 R² is -N(R⁷)C(O)R⁸, -(C₁₋₂alkylene)-N(R⁷)C(O)R⁸, or heteroaryl, wherein said
 heteroaryl group is optionally substituted with 1 or 2 substituents independently selected from
 the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, heteroaryl,
 and -N(R³)(R⁴);

20 R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken
 together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclic
 ring;

R⁵ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

R⁶ and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;

25 R⁸ is aryl, aralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -C(R⁶)₂-cycloalkyl, -C(R⁶)₂-
 cycloalkenyl, -C(R⁶)₂-heterocyclyl, or C₁₋₆alkyl; each of which is optionally substituted with 1,
 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋
 6alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, -S(O)_pC₁₋
 6alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

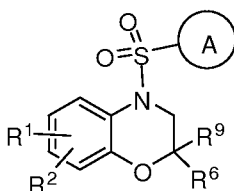
m is 1 or 2;

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p represents independently for each occurrence 0, 1, or 2; and wherein the stereochemical configuration at a stereocenter in a compound represented by Formula III-B is *R*, *S*, or a mixture thereof.

5 [0083] In certain embodiments, variables A, R¹ through R⁸, n, and p for Formula III-B are as defined by one of the further embodiments specified above in connection with Formula III-A.

[0084] Another aspect of the invention provides a compound of Formula III-C:



10

(III-C)

or a pharmaceutically acceptable salt or solvate thereof; wherein:

A is aryl or heteroaryl; each of which is substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, -CN, and -C(O)-C₁₋₆alkyl;

15 R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

R² is -N(R⁷)C(O)R⁸;

R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclic ring;

20 R⁶ and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;

R⁸ is aryl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

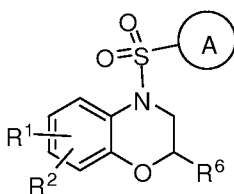
R⁹ is C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-N(R³)C(O)-C₁₋₆alkyl, -C₁₋₆alkylene-CN, or -C₁₋₆alkylene-C₁₋₆alkoxy; and

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wherein the stereochemical configuration at a stereocenter in a compound represented by Formula III-C is *R*, *S*, or a mixture thereof.

[0085] In certain embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, and -CN. In certain embodiments, R⁸ is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl. In certain embodiments, R⁸ is phenyl substituted with 2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl, where the first substituent is located at the 2-position of the phenyl group, and the second substituent is located at the 6-position of the phenyl group. In certain embodiments, R⁹ is C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, -C₁₋₆alkylene-N(R³)C(O)-C₁₋₆alkyl, or -C₁₋₆alkylene-C₁₋₆alkoxy. In certain embodiments, R² is attached to the 6-position of the benzoxazine ring.

[0086] Another aspect of the invention provides a compound of Formula III-D:



(III-D)

or a pharmaceutically acceptable salt or solvate thereof; wherein:

A is aryl or heteroaryl; each of which is substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, -CN, and -C(O)-C₁₋₆alkyl;

R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

R² is -N(R⁷)C(O)R⁸;

R⁶ is C₁₋₆alkyl;

R⁷ is hydrogen or C₁₋₆alkyl;

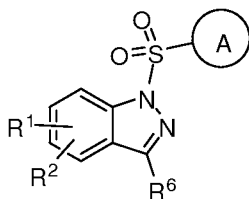
R⁸ is aryl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl; and

- 31 -

wherein the stereochemical configuration at a stereocenter in a compound represented by Formula III-D is *R*, *S*, or a mixture thereof

[0087] In certain embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, and -CN. In certain embodiments, R⁸ is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl. In certain embodiments, R⁸ is phenyl substituted with 2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl, where the first substituent is located at the 2-position of the phenyl group, and the second substituent is located at the 6-position of the phenyl group. In certain embodiments, R⁶ is methyl. In certain embodiments, R¹ and R⁷ are hydrogen. In certain embodiments, R² is attached at the 6-position of the benzoxazine ring.

[0088] Another aspect of the invention provides a compound of Formula III-E:



15

(III-E)

or a pharmaceutically acceptable salt or solvate thereof; wherein:

A is aryl or heteroaryl; each of which is substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, -CN, and -C(O)-C₁₋₆alkyl;

20 R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

R² is -N(R⁷)C(O)R⁸;

R⁶ is C₁₋₆alkyl;

R⁷ is hydrogen or C₁₋₆alkyl;

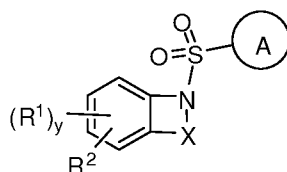
25 R⁸ is aryl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl; and

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wherein the stereochemical configuration at a stereocenter in a compound represented by Formula III-E is *R*, *S*, or a mixture thereof.

[0089] In certain embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, and -CN. In certain embodiments, R⁸ is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl. In certain embodiments, R⁸ is phenyl substituted with 2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl, where the first substituent is located at the 2-position of the phenyl group, and the second substituent is located at the 6-position of the phenyl group. In certain embodiments, R¹, R⁶, and R⁷ are hydrogen. In certain embodiments, R² is attached at the 6-position of the indazole ring.

[0090] Another aspect of the invention provides a compound of Formula III-F:



15

(III-F)

or a pharmaceutically acceptable salt or solvate thereof; wherein:

A is aryl or heteroaryl; each of which is substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-aryl, -O-C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-CO₂R⁶, -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴), -CN, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), -N(R³)SO₂(C₁₋₆alkyl), heterocyclyl, C(O)R¹¹, -C(R¹¹)(R¹²)OH, -C(O)N(R³)(R⁴), and -N(R³)C(O)N(R³)(R⁴);

X is -C(R⁶)=N-ψ or -C(R¹⁰)=N-ψ; wherein ψ is a bond to the sulfonamide ring nitrogen atom in Formula III-F;

R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

R² is -N(R⁷)C(O)R⁸ or -(C₁₋₂alkylene)-N(R⁷)C(O)R⁸;

25

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R^3 and R^4 each represent independently hydrogen or C_{1-6} alkyl; or R^3 and R^4 taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclic ring;

R^5 represents independently for each occurrence hydrogen, halogen, or C_{1-6} alkyl;

5 R^6 and R^7 each represent independently for each occurrence hydrogen or C_{1-6} alkyl;

R^8 is aryl or aralkyl; each of which is substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, $-N(R^3)(R^4)$, $-CN$, $-CO_2-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkyl, $-C(O)N(R^3)(R^4)$, $-S(O)_pC_{1-6}$ alkyl, $-SO_2N(R^3)(R^4)$, and $-N(R^3)SO_2(C_{1-6}$ alkyl);

10 R^9 and R^{10} each represent independently C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, $-C_{1-6}$ alkylene- $N(R^3)(R^4)$, $-C_{1-6}$ alkylene- $N(R^3)C(O)-C_{1-6}$ alkyl, $-C_{1-6}$ alkylene- CO_2R^3 , $-C_{1-6}$ alkylene- CN , $-C_{1-6}$ alkylene- C_{1-6} alkoxy, $-C_{1-6}$ alkylene- $C(O)N(R^3)(R^4)$, $-C(O)N(R^3)(R^4)$, $-C_{1-6}$ alkylene- $N(R^3)C(O)N(R^3)(R^4)$, $-C_{1-6}$ alkylene- $N(R^3)C(O)-[C(OH)(R^3)(R^4)]$, $-C_{1-6}$ alkylene- $O-C(O)N(R^3)(R^4)$, $-C_{1-6}$ alkylene- $SO_2N(R^3)(R^4)$, $-C_{1-6}$ alkylene- $N(R^3)SO_2N(R^3)(R^4)$, C_{2-4} alkenyl, 15 $-arylene-CO_2R^6$, or $-CN$;

R^{11} is C_{1-6} alkyl, C_{1-6} haloalkyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl; each of which is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, hydroxyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-CO_2R^3$, and, $-N(R^3)(R^4)$;

20 R^{12} is hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl; each of which is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, hydroxyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-CO_2R^3$, and, $-N(R^3)(R^4)$;

m is 1 or 2;

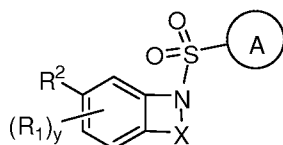
25 p represents independently for each occurrence 0, 1, or 2;

y is 1 or 2; and

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wherein the stereochemical configuration at a stereocenter in a compound represented by Formula III-F is *R*, *S*, or a mixture thereof.

[0091] Another aspect of the invention provides a compound of Formula IV:



5

(IV)

or a pharmaceutically acceptable salt or solvate thereof; wherein:

A is aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴), -CN, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), -N(R³)SO₂(C₁₋₆alkyl), heterocyclyl, -C(O)R¹¹, -C(R¹¹)(R¹²)OH, -C(O)N(R³)(R⁴), and -N(R³)C(O)N(R³)(R⁴);

15 X is -C(R⁵)₂C(R⁶)=C(R⁶)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, -C(O)-[C(R⁶)₂]_m-ψ, -C(R⁶)₂C(O)C(R⁶)₂-ψ, -[C(R⁶)₂]_m-C(O)-ψ, -C(R⁶)=C(R⁶)C(O)-ψ, -C(O)C(R⁶)=C(R⁶)-ψ, -O-[C(R⁶)₂]_m-ψ, -O-[C(R⁶)(R⁹)C(R⁶)₂]-ψ, -O-[C(R⁶)(R⁹)]-ψ, -O-[C(R⁶)₂-C(hydroxyC₁₋₆alkyl)(R⁶)]-ψ, -C(R⁶)=N-ψ, -C(R¹⁰)=N-ψ, or -C(H)(OR⁶)-[C(R⁶)₂]_m-ψ; wherein ψ is a bond to the sulfonamide ring nitrogen atom in Formula IV;

20 R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

R² is -C(O)N(R⁷)(R⁸) or -N(R⁷)C(O)N(R⁷)(R⁸);

R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclic ring;

25 R⁵ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

R⁶ and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;

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R^8 is aryl, aralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, $-C(R^6)_2$ -cycloalkyl, $-C(R^6)_2$ -cycloalkenyl, $-C(R^6)_2$ -heterocyclyl, or C_{1-6} alkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, $-N(R^3)(R^4)$, $-CN$, $-CO_2-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkyl, $-C(O)N(R^3)(R^4)$, $-S(O)_pC_{1-6}$ alkyl, $-SO_2N(R^3)(R^4)$, and $-N(R^3)SO_2(C_{1-6}alkyl)$;

R^9 and R^{10} each represent independently C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, $-C_{1-6}alkylene-N(R^3)(R^4)$, $-C_{1-6}alkylene-N(R^3)C(O)-C_{1-6}alkyl$, $-C_{1-6}alkylene-CO_2R^3$, $-C_{1-6}alkylene-CN$, $-C_{1-6}alkylene-C_{1-6}alkoxy$, $-C_{1-6}alkylene-C(O)N(R^3)(R^4)$, $-C(O)N(R^3)(R^4)$, $-C_{1-6}alkylene-N(R^3)C(O)N(R^3)(R^4)$, $-C_{1-6}alkylene-N(R^3)C(O)-[C(OH)(R^3)(R^4)]$, $-C_{1-6}alkylene-O-C(O)N(R^3)(R^4)$, $-C_{1-6}alkylene-SO_2N(R^3)(R^4)$, $-C_{1-6}alkylene-N(R^3)SO_2N(R^3)(R^4)$, $C_{2-4}alkenyl$, $-arylene-CO_2R^6$, or $-CN$;

R^{11} is C_{1-6} alkyl, C_{1-6} haloalkyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl; each of which is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, hydroxyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-CO_2R^3$, and, $-N(R^3)(R^4)$;

R^{12} is hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl; each of which is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, hydroxyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-CO_2R^3$, and, $-N(R^3)(R^4)$;

m is 1 or 2;

p represents independently for each occurrence 0, 1, or 2;

y is 1 or 2; and

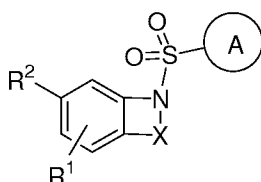
wherein the stereochemical configuration at a stereocenter in a compound represented by Formula IV is *R*, *S*, or a mixture thereof.

[0092] In certain embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, $-N(R^3)(R^4)$, $-CO_2R^6$, $-C_{1-6}alkylene-N(R^3)(R^4)$, $-C_{1-6}alkylene-C_{1-6}alkoxy$, $-C_{1-6}alkylene-CO_2R^6$, $-O-C_{1-6}alkylene-N(R^3)(R^4)$, and $-N(R^6)C(O)-C_{1-6}alkylene-N(R^3)(R^4)$. In certain embodiments, R^8 is aryl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, and C_{1-6} haloalkyl. In certain embodiments, R^8 is phenyl

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substituted with 2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl, where the first substituent is located at the 2-position of the phenyl group, and the second substituent is located at the 6-position of the phenyl group. In certain embodiments, y is 1.

- 5 [0093] Another aspect of the invention provides a compound of Formula IV-A:



(IV-A)

or a pharmaceutically acceptable salt or solvate thereof; wherein:

A is aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl; each of which is
 10 optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴), -CN, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

15 X is -C(R⁵)₂C(R⁶)=C(R⁸)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, -C(O)-[C(R⁶)₂]_m-ψ, -C(R⁶)₂C(O)C(R⁶)₂-ψ, -[C(R⁶)₂]_m-C(O)-ψ, -C(R⁶)=C(R⁶)C(O)-ψ, -C(O)C(R⁶)=C(R⁶)-ψ, or -C(H)(OR⁶)-[C(R⁶)₂]_m-ψ; wherein ψ is a bond to the sulfonamide ring nitrogen atom in Formula IV-A;

R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

20 R² is -C(O)N(R⁷)(R⁸);

R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclic ring;

R⁵ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

25 R⁶ and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;

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R^8 is aryl, aralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, $-C(R^6)_2$ -cycloalkyl, $-C(R^6)_2$ -cycloalkenyl, $-C(R^6)_2$ -heterocyclyl, or C_{1-6} alkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, $-N(R^3)(R^4)$, $-CN$, $-CO_2-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkyl, $-S(O)_pC_{1-6}$ alkyl, $-SO_2N(R^3)(R^4)$, and $-N(R^3)SO_2(C_{1-6}alkyl)$;

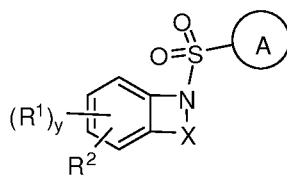
m is 1 or 2;

p represents independently for each occurrence 0, 1, or 2; and

wherein the stereochemical configuration at a stereocenter in a compound represented by Formula IV-A is *R*, *S*, or a mixture thereof.

10 **[0094]** In certain embodiments, A is phenyl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, $-N(R^3)(R^4)$, $-CO_2R^6$, $-C_{1-6}alkylene-N(R^3)(R^4)$, $-C_{1-6}alkylene-C_{1-6}alkoxy$, $-C_{1-6}alkylene-CO_2R^6$, $-O-C_{1-6}alkylene-N(R^3)(R^4)$, and $-N(R^6)C(O)-C_{1-6}alkylene-N(R^3)(R^4)$. In certain embodiments, R^8 is aryl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, $-N(R^3)(R^4)$, $-CN$, $-CO_2-C_{1-6}alkyl$, $-C(O)-C_{1-6}alkyl$, and $-S-C_{1-6}alkyl$. In certain embodiments, R^8 is phenyl substituted with 2 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, and C_{1-6} haloalkyl, where the first substituent is located at the 2-position of the phenyl group, and the second substituent is located at the 6-position of the phenyl group. In 20 certain embodiments, X is $-C(O)-[C(R^6)_2]_m-\psi$, $-C(R^6)_2C(O)C(R^6)_2-\psi$, $-[C(R^6)_2]_m-C(O)-\psi$, $-C(R^6)=C(R^6)C(O)-\psi$, or $-C(O)C(R^6)=C(R^6)-\psi$.

[0095] Another aspect of the invention provides a compound represented by Formula V:



25

(V)

or a pharmaceutically acceptable salt or solvate thereof; wherein:

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A is aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-aryl, -O-C₁₋₆alkylene-N(R³)(R⁴), -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴), -CN, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), -N(R³)SO₂(C₁₋₆alkyl), heterocyclyl, -C(O)R¹¹, -C(R¹¹)(R¹²)OH, -C(O)N(R³)(R⁴), and -N(R³)C(O)N(R³)(R⁴);

X is -[C(R⁵)₂]_n-ψ, -C(R⁵)₂C(R⁶)=C(R⁶)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, -C(R⁶)=C(R⁶)-ψ, -O-[C(R⁶)₂]_m-ψ, -O-[C(R⁶)(R⁹)C(R⁶)₂]-ψ, -O-[C(R⁶)(R⁹)]-ψ, -O-[C(R⁶)₂-C(hydroxyC₁₋₆alkyl)(R⁶)]-ψ, -N(R⁶)-[C(R⁶)₂]_m-ψ, -N=C(R⁶)-ψ, -N=C(R⁶)C(R⁶)₂-ψ, -N=N-ψ, -C(R⁶)=N-ψ, -C(R¹⁰)=N-ψ, -C(R⁶)₂C(O)C(R⁶)₂-ψ, -[C(R⁶)₂]_m-C(O)-ψ, -C(R⁶)=C(R⁶)C(O)-ψ, -C(O)C(R⁶)=C(R⁶)-ψ, -N(R⁶)-C(O)-ψ, or -C(H)(OR⁶)-[C(R⁶)₂]_m-ψ; wherein ψ is a bond to the sulfonamide ring nitrogen atom in Formula V;

R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

R² is -N(R⁷)C(O)R⁸, -(C₁₋₂alkylene)-N(R⁷)C(O)R⁸, -N(R⁷)C(O)N(R⁷)(R⁸), or heteroaryl, wherein said heteroaryl group is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, heteroaryl, and -N(R³)(R⁴);

R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclic ring;

R⁵ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

R⁶ and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;

R⁸ is aryl, aralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -C(R⁶)₂-cycloalkyl, -C(R⁶)₂-cycloalkenyl, -C(R⁶)₂-heterocyclyl, or C₁₋₆alkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, -C(O)N(R³)(R⁴), -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

R⁹ and R¹⁰ each represent independently C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-N(R³)C(O)-C₁₋₆alkyl, -C₁₋₆alkylene-CO₂R³, -C₁₋₆alkylene-CN, -C₁₋

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₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-C(O)N(R³)(R⁴), -C(O)N(R³)(R⁴), -C₁₋₆alkylene-N(R³)C(O)N(R³)(R⁴), -C₁₋₆alkylene-N(R³)C(O)-[C(OH)(R³)(R⁴)], -C₁₋₆alkylene-O-C(O)N(R³)(R⁴), -C₁₋₆alkylene-SO₂N(R³)(R⁴), -C₁₋₆alkylene-N(R³)SO₂N(R³)(R⁴), C₂₋₄alkenyl, -arylene-CO₂R⁶, or -CN;

5 R¹¹ is C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl; each of which is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, hydroxyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, -CO₂R³, and -N(R³)(R⁴);

 R¹² is hydrogen, C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl; each of which is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, hydroxyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, -CO₂R³, and, -N(R³)(R⁴);

n is 1, 2, or 3;

m is 1 or 2;

15 p represents independently for each occurrence 0, 1, or 2;

y is 1 or 2; and

wherein the stereochemical configuration at a stereocenter in a compound represented by Formula V is *R*, *S*, or a mixture thereof.

[0096] In certain embodiments, A is aryl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴). In certain other embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂R⁶, -C(O)-C₁₋₆alkyl, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴). In yet other embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen and C₁₋₆haloalkyl. In still other embodiments, A is phenyl substituted at the 4-position with fluorine or chlorine.

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[0097] In certain other embodiments, X is $-[C(R^5)_2]_n-\psi$, $-C(R^5)_2C(R^6)=C(R^6)-\psi$, $-C(R^6)=C(R^6)C(R^5)_2-\psi$, or $-C(R^6)=C(R^6)-\psi$. In certain other embodiments, X is $-O-[C(R^6)_2]_m-\psi$ or $-O-[C(R^6)(R^9)C(R^6)_2]-\psi$. In certain other embodiments, X is $-C(R^6)=N-\psi$ or $-C(R^{10})=N-\psi$.

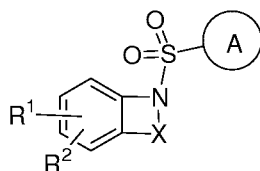
5 [0098] In certain other embodiments, X is $-(CH_2)_3-\psi$. In certain embodiments, R² is attached to the 7-position of the tetrahydroquinoline ring.

[0099] In certain embodiments, R² is $-N(R^7)C(O)R^8$.

[0100] In certain embodiments, R⁸ is aryl or aralkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen,
 10 hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, $-N(R^3)(R^4)$, $-CN$, $-CO_2-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkyl, and $-S-C_{1-6}$ alkyl. In certain other embodiments, R⁸ is aryl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl. In certain other embodiments, R⁸ is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl. In
 15 certain embodiments, R⁸ is phenyl substituted with 2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl, where the first substituent is located at the 2-position of the phenyl group, and the second substituent is located at the 6-position of the phenyl group.

[0101] In certain embodiments, y is 1.

20 [0102] Another aspect of the invention provides a compound represented by Formula V-A:



(V-A)

or a pharmaceutically acceptable salt or solvate thereof; wherein:

A is aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl; each of which is
 25 optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, $-N(R^3)(R^4)$, $-CO_2R^6$, $-C_{1-6}$ alkylene- $N(R^3)(R^4)$, -

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C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴), -CN, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

X is -[C(R⁵)₂]_n-ψ, -C(R⁵)₂C(R⁶)=C(R⁸)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, -C(R⁶)=C(R⁶)-ψ, -O-[C(R⁶)₂]_m-ψ, -N(R⁶)-[C(R⁶)₂]_m-ψ, -N=C(R⁶)-ψ, -N=C(R⁶)C(R⁶)₂-ψ, -N=N-ψ, -C(R⁶)=N-ψ, -C(O)-[C(R⁶)₂]_m-ψ, -C(R⁶)₂C(O)C(R⁶)₂-ψ, -[C(R⁶)₂]_m-C(O)-ψ, -C(R⁶)=C(R⁶)C(O)-ψ, -C(O)C(R⁶)=C(R⁶)-ψ, -N(R⁶)-C(O)-ψ, or -C(H)(OR⁶)-[C(R⁶)₂]_m-ψ; wherein ψ is a bond to the sulfonamide ring nitrogen atom in Formula V-A;

R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

R² is -N(R⁷)C(O)R⁸, -(C₁₋₂alkylene)-N(R⁷)C(O)R⁸, or heteroaryl, wherein said heteroaryl group is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, heteroaryl, and -N(R³)(R⁴);

R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclic ring;

R⁵ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

R⁶ and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;

R⁸ is aryl, aralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -C(R⁶)₂-cycloalkyl, -C(R⁶)₂-cycloalkenyl, -C(R⁶)₂-heterocyclyl, or C₁₋₆alkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

n is 1, 2, or 3;

m is 1 or 2;

p represents independently for each occurrence 0, 1, or 2; and

wherein the stereochemical configuration at a stereocenter in a compound represented by Formula V-A is *R*, *S*, or a mixture thereof.

[0103] In certain embodiments, A is aryl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl,

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-N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴). In certain embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen and C₁₋₆haloalkyl. In certain embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, and -N(R³)(R⁴). In certain embodiments, A is phenyl substituted at the 4-position with fluorine or chlorine.

[0104] In certain embodiments, X is -[C(R⁵)₂]_n-ψ, -C(R⁵)₂C(R⁶)=C(R⁸)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, or -C(R⁶)=C(R⁶)-ψ. In certain embodiments, X is -(CH₂)₃-ψ. In certain embodiments, X is -(CH₂)₃-ψ, and R² is attached to the 7-position of the tetrahydroquinoline ring. In certain embodiments, X is -O-[C(R⁶)₂]_m-ψ, -N(R⁶)-[C(R⁶)₂]_m-ψ, -N=C(R⁶)-ψ, or -N=C(R⁶)C(R⁶)₂-ψ. In certain embodiments, X is -C(O)-[C(R⁶)₂]_m-ψ, -C(R⁶)₂C(O)C(R⁶)₂-ψ, -[C(R⁶)₂]_m-C(O)-ψ, -C(R⁶)=C(R⁶)C(O)-ψ, -C(O)C(R⁶)=C(R⁶)-ψ, or -N(R⁶)-C(O)-ψ. In certain embodiments, X is -C(O)-[C(R⁶)₂]_m-ψ.

[0105] In certain embodiments, R² is -N(R⁷)C(O)R⁸. In certain embodiments, R² is -(C₁₋₂alkylene)-N(R⁷)C(O)R⁸ or -C(O)N(R⁷)(R⁸). In certain embodiments, R² is a heteroaryl group optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, and -N(R³)(R⁴).

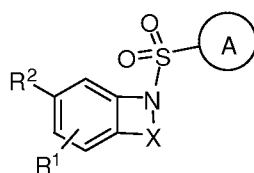
[0106] In certain embodiments, R⁸ is aryl or aralkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, and -S-C₁₋₆alkyl.

[0107] In certain embodiments, R⁸ is aryl or aralkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, and -CO₂-C₁₋₆alkyl. In certain embodiments, R⁸ is phenyl substituted with 2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl, where the first substituent is located at the 2-position of the phenyl group, and the second substituent is located at the 6-position of the phenyl group. In certain embodiments, R⁸ is an aromatic heterocyclyl or -C(R⁶)₂-(aromatic heterocyclyl); each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl,

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-N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, and -S-C₁₋₆alkyl. In certain embodiments, R⁸ is cycloalkyl, cycloalkenyl, heterocyclyl, -C(R⁶)₂-cycloalkyl, -C(R⁶)₂-cycloalkenyl, -C(R⁶)₂-heterocyclyl, or C₁₋₆alkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, and -S-C₁₋₆alkyl. In certain embodiments, R⁸ is C₁₋₆alkyl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, and -C(O)-C₁₋₆alkyl.

10 **[0108]** Another aspect of the invention provides a compound represented by Formula V-B:



(V-B)

or a pharmaceutically acceptable salt or solvate thereof; wherein:

A is aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴), -CN, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

20 X is -[C(R⁵)₂]_n-ψ, -C(R⁵)₂C(R⁶)=C(R⁸)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, -C(R⁶)=C(R⁶)-ψ, -O-[C(R⁶)₂]_m-ψ, -N(R⁶)-[C(R⁶)₂]_m-ψ, -N=C(R⁶)-ψ, -N=C(R⁶)C(R⁶)₂-ψ, -N=N-ψ, -C(R⁶)=N-ψ, -C(O)-[C(R⁶)₂]_m-ψ, -C(R⁶)₂C(O)C(R⁶)₂-ψ, -[C(R⁶)₂]_m-C(O)-ψ, -C(R⁶)=C(R⁶)C(O)-ψ, -C(O)C(R⁶)=C(R⁶)-ψ, -N(R⁶)-C(O)-ψ, or -C(H)(OR⁶)-[C(R⁶)₂]_m-ψ; wherein ψ is a bond to the sulfonamide ring nitrogen atom in Formula V-B;

25 R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

R² is -N(R⁷)C(O)R⁸, -(C₁₋₂alkylene)-N(R⁷)C(O)R⁸, or heteroaryl, wherein said heteroaryl group is optionally substituted with 1 or 2 substituents independently selected from

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the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, heteroaryl, and -N(R³)(R⁴);

R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclic ring;

R⁵ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

R⁶ and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;

R⁸ is aryl, aralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -C(R⁶)₂-cycloalkyl, -C(R⁶)₂-cycloalkenyl, -C(R⁶)₂-heterocyclyl, or C₁₋₆alkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

n is 1, 2, or 3;

m is 1 or 2;

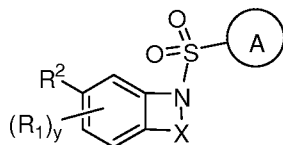
p represents independently for each occurrence 0, 1, or 2; and

wherein the stereochemical configuration at a stereocenter in a compound represented by Formula V-B is *R*, *S*, or a mixture thereof.

[0109] In certain embodiments, variables A, R¹ through R⁸, n, and p for Formula V-B are as defined by one of the further embodiments specified above in connection with Formula V-A.

20

[0110] Another aspect of the invention provides a compound represented by Formula VI:



(VI)

or a pharmaceutically acceptable salt or solvate thereof; wherein:

A is aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group

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- 45 -

consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-aryl, -O-C₁₋₆alkylene-N(R³)(R⁴), -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴), -CN, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), -N(R³)SO₂(C₁₋₆alkyl), heterocyclyl, -C(O)R¹¹, -C(R¹¹)(R¹²)OH, -C(O)N(R³)(R⁴), and -N(R³)C(O)N(R³)(R⁴);

X is -[C(R⁵)₂]₃-ψ, -C(R⁵)₂C(R⁶)=C(R⁶)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, -C(R⁶)=C(R⁶)-ψ, -C(O)-[C(R⁶)₂]_m-ψ, -C(R⁶)₂C(O)C(R⁶)₂-ψ, -[C(R⁶)₂]_m-C(O)-ψ, -C(R⁶)=C(R⁶)C(O)-ψ, -C(O)C(R⁶)=C(R⁶)-ψ, -C(R⁶)=N-ψ, -C(R¹⁰)=N-ψ, -O-[C(R⁶)₂]_m-ψ, -O-[C(R⁶)(R⁹)C(R⁶)₂]-ψ, -O-[C(R⁶)(R⁹)]-ψ, -O-[C(R⁶)₂-C(hydroxyC₁₋₆alkyl)(R⁶)]-ψ, or -C(H)(OR⁶)-[C(R⁶)₂]_m-ψ;

wherein ψ is a bond to the sulfonamide ring nitrogen atom in Formula VI;

R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

R² is -C(O)N(R⁷)(R⁸);

R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclic ring;

R⁵ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

R⁶ and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;

R⁸ is aryl or aralkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, and -CN;

R⁹ and R¹⁰ each represent independently C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-N(R³)C(O)-C₁₋₆alkyl, -C₁₋₆alkylene-CO₂R³, -C₁₋₆alkylene-CN, -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-C(O)N(R³)(R⁴), -C(O)N(R³)(R⁴), -C₁₋₆alkylene-N(R³)C(O)N(R³)(R⁴), -C₁₋₆alkylene-N(R³)C(O)-[C(OH)(R³)(R⁴)], -C₁₋₆alkylene-O-C(O)N(R³)(R⁴), -C₁₋₆alkylene-SO₂N(R³)(R⁴), -C₁₋₆alkylene-N(R³)SO₂N(R³)(R⁴), C₂₋₄alkenyl, -arylene-CO₂R⁶, or -CN;

R¹¹ is C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl; each of which is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, hydroxyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, -CO₂R³, and, -N(R³)(R⁴);

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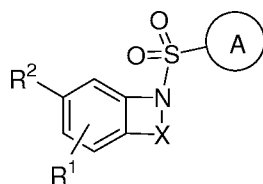
R^{12} is hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl; each of which is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, hydroxyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-CO_2R^3$, and, $-N(R^3)(R^4)$;

- 5 m is 1 or 2;
 p is 0, 1, or 2;
 y is 1 or 2; and

wherein the stereochemical configuration at a stereocenter in a compound represented by Formula VI is *R*, *S*, or a mixture thereof.

- 10 **[0111]** In certain embodiments, A is aryl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, $-N(R^3)(R^4)$, $-CO_2R^6$, $-C_{1-6}$ alkylene- $N(R^3)(R^4)$, $-C_{1-6}$ alkylene- CO_2R^6 , $-O-C_{1-6}$ alkylene- $N(R^3)(R^4)$, and $-N(R^6)C(O)-C_{1-6}$ alkylene- $N(R^3)(R^4)$. In certain other embodiments, A is phenyl substituted at the 4-position with fluorine or chlorine. In certain embodiments, R^8 is phenyl substituted with 2 or 3 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, and C_{1-6} haloalkyl. In certain embodiments, R^8 is phenyl substituted with 2 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, and C_{1-6} haloalkyl, where the first substituent is located at the 2-position of the phenyl group, and the second substituent is located at the 6-position of the phenyl group. In certain embodiments, y is
- 15
- 20 1.

[0112] Another aspect of the invention provides a compound represented by Formula VI-A:



(VI-A)

- 25 or a pharmaceutically acceptable salt or solvate thereof; wherein:

A is aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group

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consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴), -CN, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

- 5 X is -[C(R⁵)₂]₃-ψ, -C(R⁵)₂C(R⁶)=C(R⁸)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, -C(R⁶)=C(R⁶)-ψ, -C(O)-[C(R⁶)₂]_m-ψ, -C(R⁶)₂C(O)C(R⁶)₂-ψ, -[C(R⁶)₂]_m-C(O)-ψ, -C(R⁶)=C(R⁶)C(O)-ψ, -C(O)C(R⁶)=C(R⁶)-ψ, or -C(H)(OR⁶)-[C(R⁶)₂]_m-ψ; wherein ψ is a bond to the sulfonamide ring nitrogen atom in Formula VI-A;

R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

- 10 R² is -C(O)N(R⁷)(R⁸);

R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclic ring;

R⁵ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

- 15 R⁶ and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;

R⁸ is aryl or aralkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, and -CN;

m is 1 or 2;

p is 0, 1, or 2; and

- 20 wherein the stereochemical configuration at a stereocenter in a compound represented by Formula VI-A is *R*, *S*, or a mixture thereof.

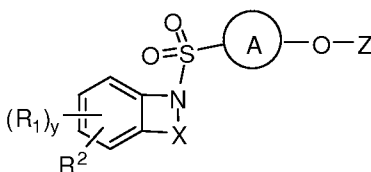
[0113] In certain embodiments, A is aryl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋

- 25 ₆alkylene-N(R³)(R⁴), and -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴). In certain embodiments, A is phenyl substituted at the 4-position with fluorine or chlorine. In certain embodiments, R⁸ is phenyl substituted with 2 or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, and -CN. In certain embodiments, R⁸ is phenyl substituted with 2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and

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C₁₋₆haloalkyl, where the first substituent is located at the 2-position of the phenyl group, and the second substituent is located at the 6-position of the phenyl group.

[0114] Another aspect of the invention provides a compound of Formula VII:



(VII)

or a pharmaceutically acceptable salt or solvate thereof; wherein:

A is arylene, aralkylene, heteroarylene, cycloalkylene, or heterocycloalkylene; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-aryl, -O-C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-CO₂R⁶, -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴), -CN, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), -N(R³)SO₂(C₁₋₆alkyl), heterocyclyl, -C(O)R¹¹, -C(R¹¹)(R¹²)OH, -C(O)N(R³)(R⁴), and -N(R³)C(O)N(R³)(R⁴);

X is -C(R⁵)(C₁₋₆alkyl)[C(R⁵)₂]_m-ψ, -[C(R⁵)₂]_m-C(R⁵)(C₁₋₆alkyl)-ψ, -C(R⁵)₂-C(R⁵)(C₁₋₆alkyl)-C(R⁵)₂-ψ, -C(R⁵)₂C(R⁶)=C(R⁶)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, -C(R⁶)=C(R⁶)-ψ, -O-[C(R⁶)₂]_m-ψ, -O-[C(R⁶)(R⁹)C(R⁶)₂]-ψ, -O-[C(R⁶)(R⁹)]-ψ, -O-[C(R⁶)₂-C(hydroxyC₁₋₆alkyl)(R⁶)]-ψ, -N(R⁶)-[C(R⁶)₂]_m-ψ, -N=C(R⁶)-ψ, -N=C(R⁶)C(R⁶)₂-ψ, -N=N-ψ, -C(R⁶)=N-ψ, -C(R¹⁰)=N-ψ, -C(O)-[C(R⁶)₂]_m-ψ, -C(R⁶)₂C(O)C(R⁶)₂-ψ, -[C(R⁶)₂]_m-C(O)-ψ, -C(R⁶)=C(R⁶)C(O)-ψ, -C(O)C(R⁶)=C(R⁶)-ψ, -N(R⁶)-C(O)-ψ, or -C(H)(OR⁶)-[C(R⁶)₂]_m-ψ;

wherein ψ is a bond to the sulfonamide ring nitrogen atom in Formula VII;

Z is C₁₋₆alkyl or C₁₋₆haloalkyl;

R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

R² is -N(R⁷)C(O)R⁸, -(C₁₋₂alkylene)-N(R⁷)C(O)R⁸, -N(R⁷)C(O)N(R⁷)(R⁸), or heteroaryl,

wherein said heteroaryl group is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, heteroaryl, and -N(R³)(R⁴);

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R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclic ring;

R⁵ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

5 R⁶ and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;

R⁸ is aryl, aralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -C(R⁶)₂-cycloalkyl, -C(R⁶)₂-cycloalkenyl, -C(R⁶)₂-heterocyclyl, or C₁₋₆alkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, -C(O)N(R³)(R⁴), -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

R⁹ and R¹⁰ each represent independently C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-N(R³)C(O)-C₁₋₆alkyl, -C₁₋₆alkylene-CO₂R³, -C₁₋₆alkylene-CN, -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-C(O)N(R³)(R⁴), -C(O)N(R³)(R⁴), -C₁₋₆alkylene-N(R³)C(O)N(R³)(R⁴), -C₁₋₆alkylene-N(R³)C(O)-[C(OH)(R³)(R⁴)], -C₁₋₆alkylene-O-C(O)N(R³)(R⁴), -C₁₋₆alkylene-SO₂N(R³)(R⁴), -C₁₋₆alkylene-N(R³)SO₂N(R³)(R⁴), C₂₋₄alkenyl, -arylene-CO₂R⁶, or -CN;

R¹¹ is C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl; each of which is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, hydroxyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, -CO₂R³, and, -N(R³)(R⁴);

R¹² is hydrogen, C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl; each of which is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, hydroxyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, -CO₂R³, and, -N(R³)(R⁴);

25 m is 1 or 2;

p represents independently for each occurrence 0, 1, or 2;

y is 1 or 2; and

wherein the stereochemical configuration at a stereocenter in a compound represented by Formula VII is *R*, *S*, or a mixture thereof.

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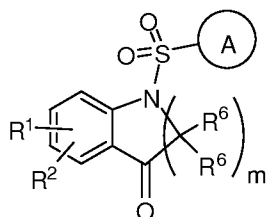
[0115] In certain embodiments, A is aryl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂R⁶, -C(O)-C₁₋₆alkyl, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴). In certain other embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂R⁶, -C(O)-C₁₋₆alkyl, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴).

[0116] In certain embodiments, X is -O-[C(R⁶)₂]_m-ψ or -O-[C(R⁶)(R⁹)C(R⁶)₂]-ψ. In certain other embodiments, X is -C(R⁶)=N-ψ or -C(R¹⁰)=N-ψ.

[0117] In certain embodiments, R² is -N(R⁷)C(O)R⁸. In certain embodiments, R⁸ is aryl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl. In certain other embodiments, R⁸ is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl. In certain embodiments, R⁸ is phenyl substituted with 2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl, where the first substituent is located at the 2-position of the phenyl group, and the second substituent is located at the 6-position of the phenyl group.

[0118] In certain embodiments, y is 1.

[0119] Another aspect of the invention provides a compound of Formula VIII:



(VIII)

or a pharmaceutically acceptable salt or solvate thereof; wherein:

A is aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋

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$_6$ alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-CO₂R⁶, -N(R⁵)C(O)-C₁₋₆alkylene-N(R³)(R⁴), -CN, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

5 R² is -N(R⁷)C(O)R⁸, -(C₁₋₂alkylene)-N(R⁷)C(O)R⁸, or heteroaryl, wherein said heteroaryl group is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, heteroaryl, and -N(R³)(R⁴);

10 R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclic ring;

R⁵, R⁶, and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;

15 R⁸ is aryl, aralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -C(R⁶)₂-cycloalkyl, -C(R⁶)₂-cycloalkenyl, -C(R⁶)₂-heterocyclyl, or C₁₋₆alkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

m is 1 or 2;

p represents independently for each occurrence 0, 1, or 2; and

20 wherein the stereochemical configuration at a stereocenter in a compound represented by Formula VIII is *R*, *S*, or a mixture thereof

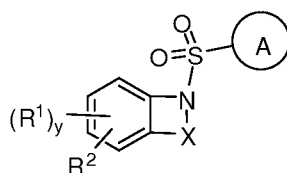
[0120] In certain embodiments, A is aryl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂R⁶, -C(O)-C₁₋₆alkyl, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R⁵)C(O)-C₁₋₆alkylene-N(R³)(R⁴). In certain other embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂R⁶, -C(O)-C₁₋₆alkyl, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R⁵)C(O)-C₁₋₆alkylene-N(R³)(R⁴).

30 **[0121]** In certain embodiments, R² is -N(R⁷)C(O)R⁸.

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[0122] In certain embodiments, R⁸ is aryl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl. In certain embodiments, R⁸ is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl. In certain
 5 embodiments, R⁸ is phenyl substituted with 2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl, where the first substituent is located at the 2-position of the phenyl group, and the second substituent is located at the 6-position of the phenyl group.

10 [0123] Another aspect of the invention provides a compound of Formula IX:



(IX)

or a pharmaceutically acceptable salt or solvate thereof; wherein:

A is aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl; each of which is
 15 optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), -O-C₁₋₆alkylene-CO₂R⁶, -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴), -O-aryl, -CN, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), -N(R³)SO₂(C₁₋₆alkyl),
 20 heterocyclyl, -C(O)R¹¹, -C(R¹¹)(R¹²)OH, -C(O)N(R³)(R⁴), and -N(R³)C(O)N(R³)(R⁴);

X is -[C(R⁵)₂]_n-ψ, -C(R⁵)₂C(R⁶)=C(R⁶)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, -C(R⁶)=C(R⁶)-ψ, -O-[C(R⁶)₂]_m-ψ, -O-[C(R⁶)(R⁹)C(R⁶)₂]-ψ, -O-[C(R⁶)(R⁹)]-ψ, -O-[C(R⁶)₂-C(hydroxyC₁₋₆alkyl)(R⁶)]-ψ, -N(R⁶)-[C(R⁶)₂]_m-ψ, -N=C(R⁶)-ψ, -N=C(R⁶)C(R⁶)₂-ψ, -N=N-ψ, -C(R⁶)=N-ψ, -C(R¹⁰)=N-ψ, -C(O)-[C(R⁶)₂]_m-ψ, -C(R⁶)₂C(O)C(R⁶)₂-ψ, -[C(R⁶)₂]_m-C(O)-ψ, -
 25 C(R⁶)=C(R⁶)C(O)-ψ, -C(O)C(R⁶)=C(R⁶)-ψ, -N(R⁶)-C(O)-ψ, or -C(H)(OR⁶)-[C(R⁶)₂]_m-ψ;
 wherein ψ is a bond to the sulfonamide ring nitrogen atom in Formula IX;

R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

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R^2 is $-N(R^7)C(O)R^8$, $-(C_{1-2}alkylene)-N(R^7)C(O)R^8$, $-C(O)N(R^7)(R^8)$, $-N(R^7)C(O)N(R^7)(R^8)$, or heteroaryl, wherein said heteroaryl group is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, hydroxyl, $C_{1-6}alkoxy$, $C_{1-6}alkyl$, $C_{1-6}haloalkyl$, aryl, heteroaryl, and $-N(R^3)(R^4)$;

5 R^3 and R^4 each represent independently hydrogen or $C_{1-6}alkyl$; or R^3 and R^4 taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclic ring;

R^5 represents independently for each occurrence hydrogen, halogen, or $C_{1-6}alkyl$;

R^6 and R^7 each represent independently for each occurrence hydrogen or $C_{1-6}alkyl$;

10 R^8 is aryl, aralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, $-C(R^6)_2-cycloalkyl$, $-C(R^6)_2-cycloalkenyl$, $-C(R^6)_2-heterocyclyl$, or $C_{1-6}alkyl$; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, $C_{1-6}alkoxy$, $C_{1-6}haloalkoxy$, $C_{1-6}alkyl$, $C_{1-6}haloalkyl$, $-N(R^3)(R^4)$, $-CN$, $-CO_2-C_{1-6}alkyl$, $-C(O)-C_{1-6}alkyl$, $-C(O)N(R^3)(R^4)$, $-S(O)_pC_{1-6}alkyl$, $-SO_2N(R^3)(R^4)$, and $-N(R^3)SO_2(C_{1-6}alkyl)$;

15 R^9 and R^{10} each represent independently $C_{1-6}haloalkyl$, $C_{1-6}hydroxyalkyl$, $-C_{1-6}alkylene-N(R^3)(R^4)$, $-C_{1-6}alkylene-N(R^3)C(O)-C_{1-6}alkyl$, $-C_{1-6}alkylene-CO_2R^3$, $-C_{1-6}alkylene-CN$, $-C_{1-6}alkylene-C_{1-6}alkoxy$, $-C_{1-6}alkylene-C(O)N(R^3)(R^4)$, $-C(O)N(R^3)(R^4)$, $-C_{1-6}alkylene-N(R^3)C(O)N(R^3)(R^4)$, $-C_{1-6}alkylene-N(R^3)C(O)-[C(OH)(R^3)(R^4)]$, $-C_{1-6}alkylene-O-C(O)N(R^3)(R^4)$, $-C_{1-6}alkylene-SO_2N(R^3)(R^4)$, $-C_{1-6}alkylene-N(R^3)SO_2N(R^3)(R^4)$, $C_{2-4}alkenyl$, $-arylene-CO_2R^6$, or $-CN$;

R^{11} is $C_{1-6}alkyl$, $C_{1-6}haloalkyl$, aryl, aralkyl, heteroaryl, or heterocycloalkyl; each of which is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, $C_{1-6}alkyl$, $C_{1-6}haloalkyl$, hydroxyl, $C_{1-6}alkoxy$, $C_{1-6}haloalkoxy$, $-CO_2R^3$, and, $-N(R^3)(R^4)$;

25 R^{12} is hydrogen, $C_{1-6}alkyl$, $C_{1-6}haloalkyl$, aryl, aralkyl, heteroaryl, or heterocycloalkyl; each of which is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, $C_{1-6}alkyl$, $C_{1-6}haloalkyl$, hydroxyl, $C_{1-6}alkoxy$, $C_{1-6}haloalkoxy$, $-CO_2R^3$, and, $-N(R^3)(R^4)$;

n is 1, 2, or 3;

30 m is 1 or 2;

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p represents independently for each occurrence 0, 1, or 2;

y is 1 or 2; and

wherein the stereochemical configuration at a stereocenter in a compound represented by Formula IX is *R*, *S*, or a mixture thereof.

5 **[0124]** In certain embodiments, A is aryl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂R⁶, -C(O)-C₁₋₆alkyl, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴). In certain other embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently
 10 selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂R⁶, -C(O)-C₁₋₆alkyl, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴). In yet other embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, and
 15 -N(R³)(R⁴). In yet other embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, and -CN. In yet other embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen and C₁₋₆haloalkyl.

[0125] In certain embodiments, X is -O-[C(R⁶)₂]_m-ψ or -O-[C(R⁶)(R⁹)C(R⁶)₂]-ψ. In certain
 20 other embodiments, X is -C(R⁶)=N-ψ or -C(R¹⁰)=N-ψ. In yet other embodiments, X is -C(R⁵)(C₁₋₆alkyl)[C(R⁵)₂]_m-ψ, -[C(R⁵)₂]_m-C(R⁵)(C₁₋₆alkyl)-ψ, -C(R⁵)₂-C(R⁵)(C₁₋₆alkyl)-C(R⁵)₂-ψ, -C(R⁵)₂C(R⁶)=C(R⁶)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, or -C(R⁶)=C(R⁶)-ψ.

[0126] In certain embodiments, X is -(CH₂)₃-ψ. In certain embodiments, R² is attached to the 7-position of the tetrahydroquinoline ring.

25 **[0127]** In certain embodiments, X is -C(O)-[C(R⁶)₂]_m-ψ.

[0128] In certain embodiments, R² is -N(R⁷)C(O)R⁸.

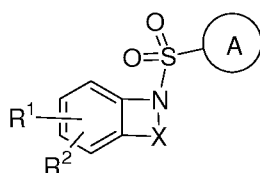
[0129] In certain embodiments, R⁸ is aryl or aralkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, and -S-C₁₋₆alkyl. In certain other embodiments, R⁸ is aryl substituted with 1, 2, or 3
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substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl. In yet other embodiments, R⁸ is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl. In certain embodiments, R⁸ is phenyl substituted with 2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl, where the first substituent is located at the 2-position of the phenyl group, and the second substituent is located at the 6-position of the phenyl group.

[0130] In certain embodiments, y is 1.

10 **[0131]** Another aspect of the invention provides a compound of Formula IX-A:



(IX-A)

or a pharmaceutically acceptable salt or solvate thereof; wherein:

A is aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), -O-C₁₋₆alkylene-CO₂R⁶, -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴), -O-aryl, -CN, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

20 X is -[C(R⁵)₂]_n-ψ, -C(R⁵)₂C(R⁶)=C(R⁸)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, -C(R⁶)=C(R⁶)-ψ, -O-[C(R⁶)₂]_m-ψ, -N(R⁶)-[C(R⁶)₂]_m-ψ, -N=C(R⁶)-ψ, -N=C(R⁶)C(R⁶)₂-ψ, -N=N-ψ, -C(R⁶)=N-ψ, -C(O)-[C(R⁶)₂]_m-ψ, -C(R⁶)₂C(O)C(R⁶)₂-ψ, -[C(R⁶)₂]_m-C(O)-ψ, -C(R⁶)=C(R⁶)C(O)-ψ, -C(O)C(R⁶)=C(R⁶)-ψ, -N(R⁶)-C(O)-ψ, or -C(H)(OR⁶)-[C(R⁶)₂]_m-ψ; wherein ψ is a bond to the sulfonamide ring nitrogen atom in Formula IX-A;

25 R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

R² is -N(R⁷)C(O)R⁸, -(C₁₋₂alkylene)-N(R⁷)C(O)R⁸, -C(O)N(R⁷)(R⁸), or heteroaryl, wherein said heteroaryl group is optionally substituted with 1 or 2 substituents independently

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selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, heteroaryl, and -N(R³)(R⁴);

R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclic ring;

R⁵ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

R⁶ and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;

R⁸ is aryl, aralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -C(R⁶)₂-cycloalkyl, -C(R⁶)₂-cycloalkenyl, -C(R⁶)₂-heterocyclyl, or C₁₋₆alkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, -S(O)_p-C₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

n is 1, 2, or 3;

m is 1 or 2;

p represents independently for each occurrence 0, 1, or 2; and

wherein the stereochemical configuration at a stereocenter in a compound represented by Formula IX-A is *R*, *S*, or a mixture thereof.

[0132] In certain embodiments, A is aryl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CO₂R¹, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴). In certain embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, and -N(R³)(R⁴). In certain embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen and C₁₋₆haloalkyl.

[0133] In certain embodiments, X -[C(R⁵)₂]_n-ψ, -C(R⁵)₂C(R⁶)=C(R⁸)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, or -C(R⁶)=C(R⁶)-ψ. In certain embodiments, X is -(CH₂)₃-ψ. In certain embodiments, X is -(CH₂)₃-ψ, and R² is attached to the 7-position of the tetrahydroquinoline ring. In certain embodiments, X is -O-[C(R⁶)₂]_m-ψ, -N(R⁶)-[C(R⁶)₂]_m-ψ, -

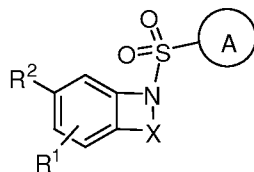
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$N=C(R^6)-\psi$, or $-N=C(R^6)C(R^6)_2-\psi$. In certain embodiments, X is $-C(O)-[C(R^6)_2]_m-\psi$, $-C(R^6)_2C(O)C(R^6)_2-\psi$, $-[C(R^6)_2]_m-C(O)-\psi$, $-C(R^6)=C(R^6)C(O)-\psi$, $-C(O)C(R^6)=C(R^6)-\psi$, or $-N(R^6)-C(O)-\psi$. In certain embodiments, X is $-C(O)-[C(R^6)_2]_m-\psi$.

[0134] In certain embodiments, R^2 is $-N(R^7)C(O)R^8$. In certain embodiments, R^2 is $-(C_{1-2}$ alkylene)- $N(R^7)C(O)R^8$ or $-C(O)N(R^7)(R^8)$. In certain embodiments, R^2 is a heteroaryl group optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and $-N(R^3)(R^4)$. In certain embodiments, R^8 is aryl or aralkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, $-N(R^3)(R^4)$, $-CN$, $-CO_2-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkyl, and $-S-C_{1-6}$ alkyl. In certain embodiments, R^8 is aryl or aralkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, $-N(R^3)(R^4)$, $-CN$, and $-CO_2-C_{1-6}$ alkyl. In certain embodiments, R^8 is phenyl substituted with 2 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, and C_{1-6} haloalkyl, where the first substituent is located at the 2-position of the phenyl group, and the second substituent is located at the 6-position of the phenyl group. In certain embodiments, R^8 is an aromatic heterocyclyl or $-C(R^6)_2$ -(aromatic heterocyclyl); each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, $-N(R^3)(R^4)$, $-CN$, $-CO_2-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkyl, and $-S-C_{1-6}$ alkyl. In certain embodiments, R^8 is cycloalkyl, cycloalkenyl, heterocyclyl, $-C(R^6)_2$ -cycloalkyl, $-C(R^6)_2$ -cycloalkenyl, $-C(R^6)_2$ -heterocyclyl, or C_{1-6} alkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, $-N(R^3)(R^4)$, $-CN$, $-CO_2-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkyl, and $-S-C_{1-6}$ alkyl. In certain embodiments, R^8 is C_{1-6} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, $-N(R^3)(R^4)$, $-CN$, $-CO_2-C_{1-6}$ alkyl, and $-C(O)-C_{1-6}$ alkyl.

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[0135] In certain embodiments, the compound is a compound of Formula IX-B:



(IX-B)

or a pharmaceutically acceptable salt or solvate thereof; wherein:

- 5 A is aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), -O-C₁₋₆alkylene-CO₂R⁶, -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴), -O-aryl, -
- 10 CN, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

- X is -[C(R⁵)₂]_n-ψ, -C(R⁵)₂C(R⁶)=C(R⁸)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, -C(R⁶)=C(R⁶)-ψ, -O-[C(R⁶)₂]_m-ψ, -N(R⁶)-[C(R⁶)₂]_m-ψ, -N=C(R⁶)-ψ, -N=C(R⁶)C(R⁶)₂-ψ, -N=N-ψ, -C(R⁶)=N-ψ, -C(O)-[C(R⁶)₂]_m-ψ, -C(R⁶)₂C(O)C(R⁶)₂-ψ, -[C(R⁶)₂]_m-C(O)-ψ, -C(R⁶)=C(R⁶)C(O)-ψ, -C(O)C(R⁶)=C(R⁶)-ψ, -N(R⁶)-C(O)-ψ, or -C(H)(OR⁶)-[C(R⁶)₂]_m-ψ; wherein ψ is a bond to the
- 15 sulfonamide ring nitrogen atom in Formula IX-B;

R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

- R² is -N(R⁷)C(O)R⁸, -(C₁₋₂alkylene)-N(R⁷)C(O)R⁸, -C(O)N(R⁷)(R⁸), or heteroaryl, wherein said heteroaryl group is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, heteroaryl, and -N(R³)(R⁴);
- 20

R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocyclic ring;

R⁵ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

- 25 R⁶ and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;

R⁸ is aryl, aralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -C(R⁶)₂-cycloalkyl, -C(R⁶)₂-cycloalkenyl, -C(R⁶)₂-heterocyclyl, or C₁₋₆alkyl; each of which is optionally substituted with 1,

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2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

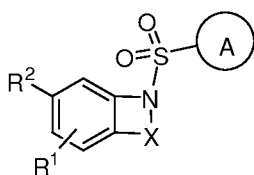
n is 1, 2, or 3;

5 m is 1 or 2;

p represents independently for each occurrence 0, 1, or 2; and

wherein the stereochemical configuration at a stereocenter in a compound represented by Formula IX-B is *R*, *S*, or a mixture thereof.

[0136] In certain embodiments, the compound is a compound of Formula IX-C:



10

(IX-C)

or a pharmaceutically acceptable salt or solvate thereof; wherein:

A is phenyl, benzyl, or pyridinyl; each of which is substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴), -CN, -S(O)₂C₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

15

X is -[C(R⁵)₂]_n-ψ, -C(R⁵)₂C(R⁶)=C(R⁸)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, -C(R⁶)=C(R⁶)-ψ, or -C(O)-[C(R⁶)₂]_m-ψ; wherein ψ is a bond to the sulfonamide ring nitrogen atom in Formula IX-

20 C;

R¹ represents independently for each occurrence hydrogen, fluoro, or methyl;

R² is -N(R⁷)C(O)R⁸ or -(CH₂)-N(R⁷)C(O)R⁸;

R³ and R⁴ each represent independently hydrogen or methyl;

R⁵ represents independently for each occurrence hydrogen, fluoro, or methyl;

25 R⁶ and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;

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R⁸ is phenyl, benzyl, or pyridinyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, -S(O)₂C₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

5 n is 1, 2, or 3;

m is 1 or 2;

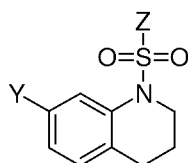
p represents independently for each occurrence 0, 1, or 2; and

wherein the stereochemical configuration at a stereocenter in a compound represented by Formula IX-C is *R*, *S*, or a mixture thereof.

10 **[0137]** The definitions of the variables in Formulae I through IX-C above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in
15 which the variables are defined by (i) or (ii).

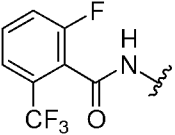
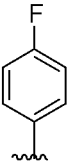
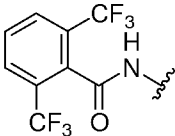
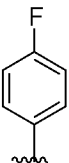
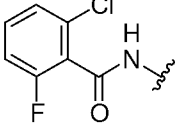
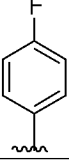
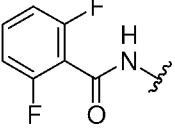
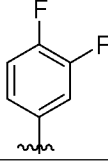
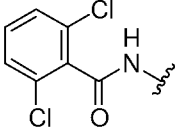
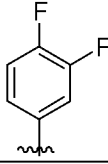
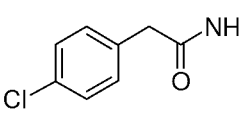
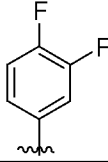
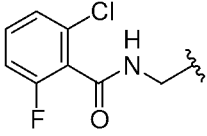
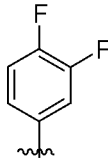
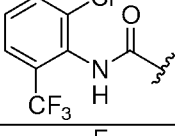
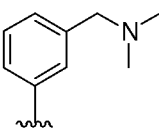
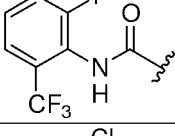
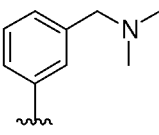
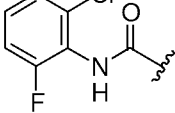
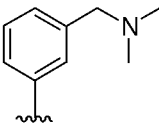
[0138] In certain other embodiments, the compound is one of the compounds listed in Tables 1 and 2 herein below, Tables 3-6 in the Examples, or a pharmaceutically acceptable salt of any of the foregoing.

TABLE 1



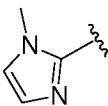

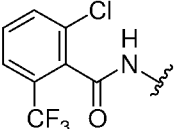
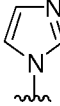
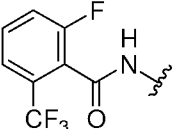
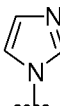
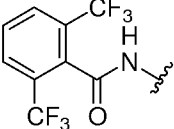
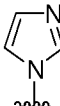
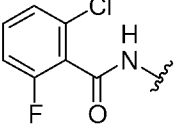
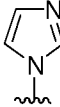
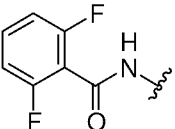
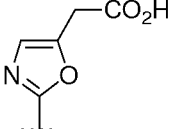
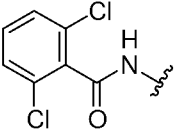
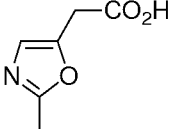
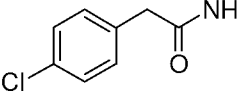
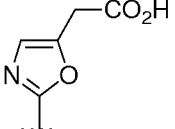
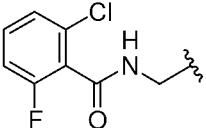
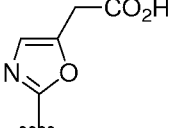
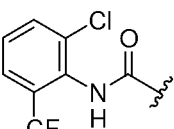
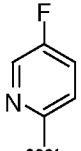
20

No.	Y	Z
I-1		

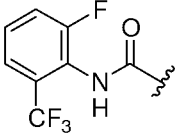
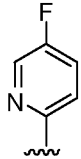
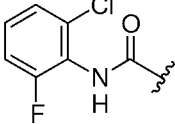
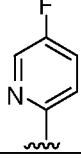
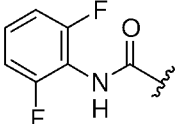
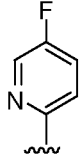
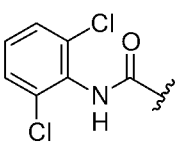
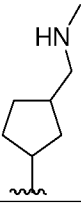
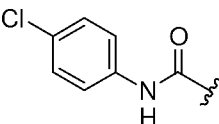
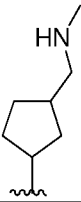
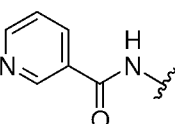
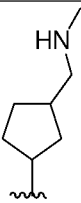
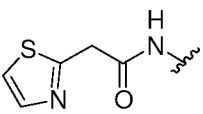
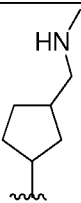
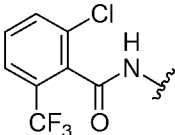
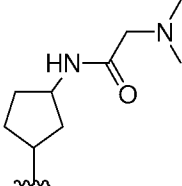
No.	Y	Z
I-2		
I-3		
I-4		
I-5		
I-6		
I-7		
I-8		
I-9		
I-10		
I-11		

No.	Y	Z
I-12		
I-13		
I-14		
I-15		
I-16		
I-17		
I-18		
I-19		

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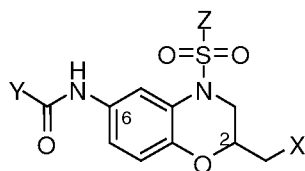
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I-20		
I-21		
I-22		
I-23		
I-24		
I-25		
I-26		
I-27		
I-28		
I-29		

- 64 -

No.	Y	Z
I-30		
I-31		
I-32		
I-33		
I-34		
I-35		
I-36		
I-37		

No.	Y	Z
I-38		
I-39		
I-40		

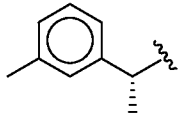
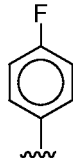
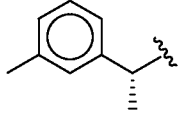
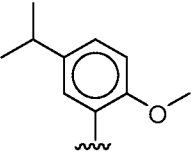
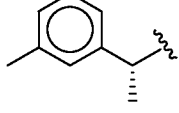
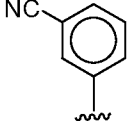
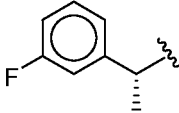
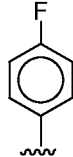
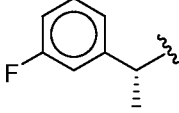
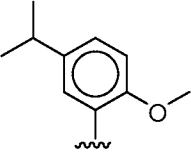
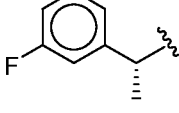
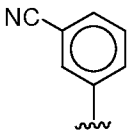
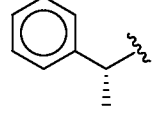
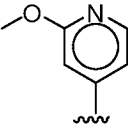
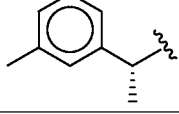
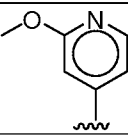
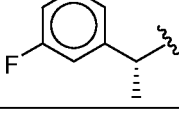
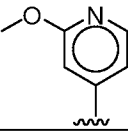
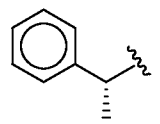
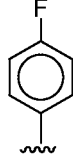
TABLE 1A



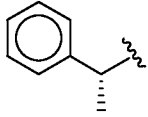
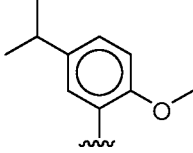
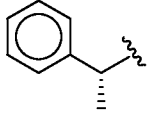
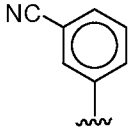
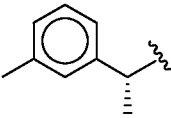
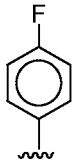
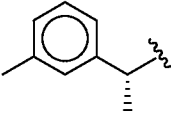
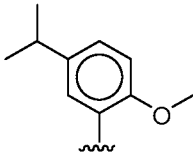
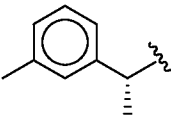
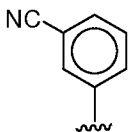
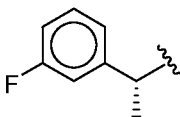
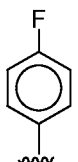
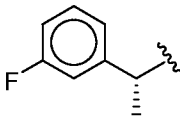
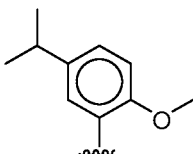
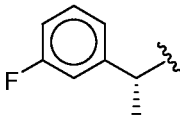
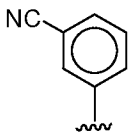
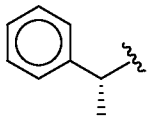
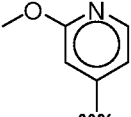
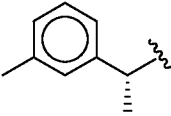
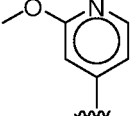
5

No.	Y	Z	X
IA-1			-OH
IA-2			-OH
IA-3			-OH

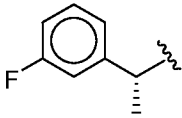
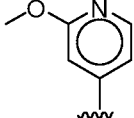
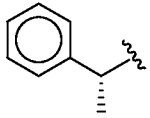
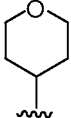
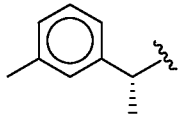
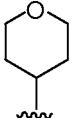
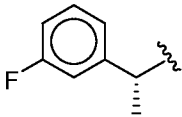
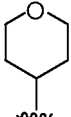
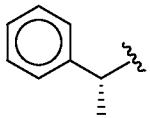
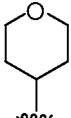
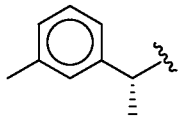
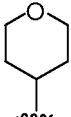
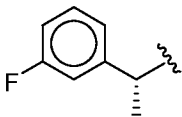
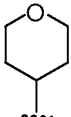
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No.	Y	Z	X
IA-4			-OH
IA-5			-OH
IA-6			-OH
IA-7			-OH
IA-8			-OH
IA-9			-OH
IA-10			-OH
IA-11			-OH
IA-12			-OH
IA-13			-N(H)C(O)CH ₃

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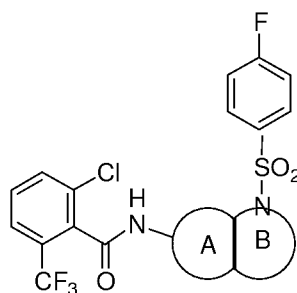
No.	Y	Z	X
IA-14			-N(H)C(O)CH ₃
IA-15			-N(H)C(O)CH ₃
IA-16			-N(H)C(O)CH ₃
IA-17			-N(H)C(O)CH ₃
IA-18			-N(H)C(O)CH ₃
IA-19			-N(H)C(O)CH ₃
IA-20			-N(H)C(O)CH ₃
IA-21			-N(H)C(O)CH ₃
IA-22			-N(H)C(O)CH ₃
IA-23			-N(H)C(O)CH ₃

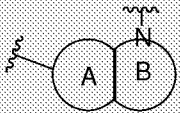
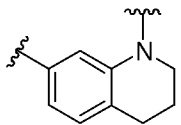
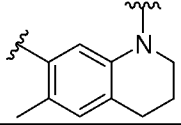
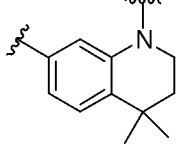
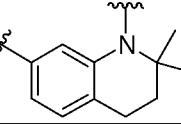
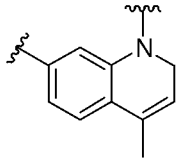
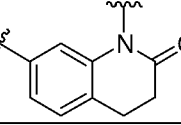
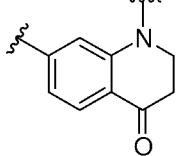
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No.	Y	Z	X
IA-24			-N(H)C(O)CH ₃
IA-25			-N(H)C(O)CH ₃
IA-26			-N(H)C(O)CH ₃
IA-27			-N(H)C(O)CH ₃
IA-28			-OH
IA-29			-OH
IA-30			-OH

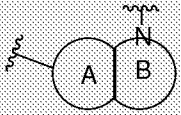
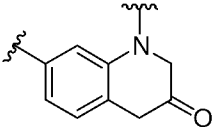
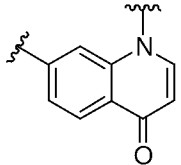
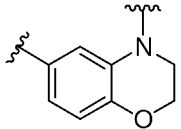
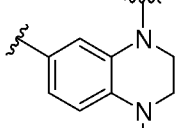
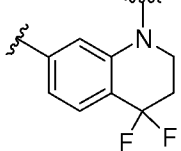
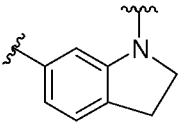
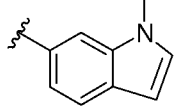
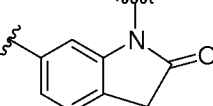
[0139] In certain embodiments, the invention provides a compound in Table 1A, where the compound has the *R*-configuration at the C3-position. In certain other embodiments, the invention provides a compound in Table 1A, where the compound has the *S*-configuration at the C3-position.

TABLE 2



No.	
II-1	
II-2	
II-3	
II-4	
II-5	
II-6	
II-7	

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No.	
II-8	
II-9	
II-10	
II-11	
II-12	
II-13	
II-14	
II-15	

[0140] In certain other embodiments, the compound is one of the following: 2-chloro-6-fluoro-N-(1-((3-(1-(methylamino)ethyl)phenyl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)benzamide; 2-chloro-N-(1-((3-((dimethylamino)methyl)phenyl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)-6-fluorobenzamide; 2-chloro-6-fluoro-N-(1-((3-(2-(methylamino)ethyl)phenyl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)benzamide; 2-chloro-N-(1-((4-(2-(dimethylamino)ethoxy)phenyl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)-6-

fluorobenzamide; N-(1-((1H-imidazol-1-yl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)-2-chloro-6-fluorobenzamide; 2-(2-((7-(2-chloro-6-fluorobenzamido)-3,4-dihydroquinolin-1(2H)-yl)sulfonyl)oxazol-5-yl)acetic acid; 2-chloro-N-(1-((4-((dimethylamino)methyl)phenyl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)-6-fluorobenzamide;

5 2-chloro-N-(1-((4-(2-(dimethylamino)ethoxy)phenyl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)-6-fluorobenzamide; 2-chloro-N-(1-((5-(2-(dimethylamino)ethoxy)-1,2,4-oxadiazol-3-yl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)-6-fluorobenzamide; 2-chloro-6-fluoro-N-(1-((4-(methylamino)cyclohexyl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)benzamide; 2-chloro-6-fluoro-N-(1-((4-hydroxycyclohexyl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)benzamide; 2-

10 chloro-6-fluoro-N-(1-((3-(methylamino)pyrrolidin-1-yl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)benzamide; 4-((7-(2-chloro-6-fluorobenzamido)-3,4-dihydroquinolin-1(2H)-yl)sulfonyl)benzoic acid; 2-chloro-6-fluoro-N-(1-((2-((methylamino)methyl)cyclopropyl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)benzamide; 2-chloro-6-fluoro-N-(1-((3-((methylamino)methyl)cyclopentyl)sulfonyl)-1,2,3,4-

15 tetrahydroquinolin-7-yl)benzamide; 2-chloro-N-(1-((3-(2-(dimethylamino)acetamido)pyrrolidin-1-yl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)-6-fluorobenzamide; N-(1-((1H-imidazol-1-yl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)-2-(4-chlorophenyl)acetamide; 2-(2-((7-(2-(4-chlorophenyl)acetamido)-3,4-dihydroquinolin-1(2H)-yl)sulfonyl)oxazol-5-yl)acetic acid; 2-(4-chlorophenyl)-N-(1-((4-

20 ((dimethylamino)methyl)phenyl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)acetamide; 2-(4-chlorophenyl)-N-(1-((4-(2-(dimethylamino)ethoxy)phenyl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)acetamide; N-(1-((1H-imidazol-1-yl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)-2-(thiazol-2-yl)acetamide; 2-(2-((7-(2-cyclohexylacetamido)-3,4-dihydroquinolin-1(2H)-yl)sulfonyl)oxazol-5-yl)acetic acid; 2-(4-methoxyphenyl)-N-(1-((4-

25 ((dimethylamino)methyl)phenyl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)acetamide; N-(1-((4-(2-(dimethylamino)ethoxy)phenyl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)-2-(p-tolyl)acetamide; 2,6-difluoro-N-(6-methyl-1-((3-(1-(methylamino)ethyl)phenyl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)benzamide; N-(1-((3-((dimethylamino)methyl)phenyl)sulfonyl)-6-methyl-1,2,3,4-tetrahydroquinolin-7-yl)-2,6-

30 difluorobenzamide; 2,6-difluoro-N-(6-methyl-1-((3-(2-(methylamino)ethyl)phenyl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)benzamide; N-(1-((4-(2-(dimethylamino)ethoxy)phenyl)sulfonyl)-6-methyl-1,2,3,4-tetrahydroquinolin-7-yl)-2,6-difluorobenzamide; 2-chloro-6-fluoro-N-(1-((4-fluorophenyl)sulfonyl)-3-methyl-1,2,3,4-

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tetrahydroquinolin-7-yl)benzamide; 2-chloro-N-(1-((3,4-difluorophenyl)sulfonyl)-4-methyl-1,2,3,4-tetrahydroquinolin-7-yl)-6-fluorobenzamide; 2,6-difluoro-N-(4-methyl-1-((5-methylisoxazol-4-yl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)benzamide; N-(1-((4-(2-(dimethylamino)ethoxy)phenyl)sulfonyl)-2-methyl-1,2,3,4-tetrahydroquinolin-7-yl)-2,6-difluorobenzamide; N-(2,6-difluorophenyl)-1-((4-methyl-3-((methylamino)methyl)phenyl)sulfonyl)-1,2,3,4-tetrahydroquinoline-7-carboxamide; N-(2,6-difluorophenyl)-1-((3-((dimethylamino)methyl)phenyl)sulfonyl)-1,2,3,4-tetrahydroquinoline-7-carboxamide; N-(2,6-difluorophenyl)-1-((3-(2-methoxyethyl)phenyl)sulfonyl)-1,2,3,4-tetrahydroquinoline-7-carboxamide; N-(2,6-difluorophenyl)-1-((4-(2-(dimethylamino)ethoxy)phenyl)sulfonyl)-1,2,3,4-tetrahydroquinoline-7-carboxamide; 1-((4-fluorophenyl)sulfonyl)-7-(1H-imidazol-1-yl)-1,2,3,4-tetrahydroquinoline; 2-(2-((6-(1H-pyrazol-5-yl)-3,4-dihydroquinolin-1(2H)-yl)sulfonyl)oxazol-5-yl)acetic acid; 1-(4-((7-(1H-imidazol-1-yl)-3,4-dihydroquinolin-1(2H)-yl)sulfonyl)phenyl)-N,N-dimethylmethanamine; 1-((3,4-difluorophenyl)sulfonyl)-6-(1H-imidazol-1-yl)-1,2,3,4-tetrahydroquinoline; 2-chloro-6-fluoro-N-(1-((4-fluorophenyl)sulfonyl)-2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)benzamide; 2-chloro-N-(1-((3-((dimethylamino)methyl)phenyl)sulfonyl)-2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)-6-fluorobenzamide; 2-chloro-N-(1-((3,4-difluorophenyl)sulfonyl)-2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)-6-fluorobenzamide; N-(1-((4-(2-(dimethylamino)ethoxy)phenyl)sulfonyl)-2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)-2,6-difluorobenzamide; 2-chloro-6-fluoro-N-(1-((4-fluorophenyl)sulfonyl)-4-methyl-1,2-dihydroquinolin-7-yl)benzamide; 2-chloro-N-(1-((3,4-difluorophenyl)sulfonyl)-4-methyl-1,2-dihydroquinolin-7-yl)-6-fluorobenzamide; N-(1-((4-(2-(dimethylamino)ethoxy)phenyl)sulfonyl)-4-methyl-1,2-dihydroquinolin-7-yl)-2,6-difluorobenzamide; 2-chloro-6-fluoro-N-(4-methyl-1-tosyl-1,2-dihydroquinolin-7-yl)benzamide; 2,6-difluoro-N-(1-((4-methyl-3-((methylamino)methyl)phenyl)sulfonyl)-4-oxo-1,2,3,4-tetrahydroquinolin-7-yl)benzamide; N-(1-((3-((dimethylamino)methyl)phenyl)sulfonyl)-4-oxo-1,2,3,4-tetrahydroquinolin-7-yl)-2,6-difluorobenzamide; 2-chloro-6-fluoro-N-(1-((4-fluorophenyl)sulfonyl)-4-oxo-1,2,3,4-tetrahydroquinolin-7-yl)benzamide; 2-chloro-N-(1-((3,4-difluorophenyl)sulfonyl)-4-oxo-1,2,3,4-tetrahydroquinolin-7-yl)-6-fluorobenzamide; 2,6-difluoro-N-(1-((4-methyl-3-((methylamino)methyl)phenyl)sulfonyl)-4-oxo-1,4-dihydroquinolin-7-yl)benzamide; N-(1-((3-((dimethylamino)methyl)phenyl)sulfonyl)-4-oxo-1,4-dihydroquinolin-7-yl)-2,6-difluorobenzamide; 2-chloro-6-fluoro-N-(1-((4-fluorophenyl)sulfonyl)-4-oxo-1,4-

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dihydroquinolin-7-yl)benzamide; 2-chloro-N-(1-((3,4-difluorophenyl)sulfonyl)-4-oxo-1,4-dihydroquinolin-7-yl)-6-fluorobenzamide; 4-chloro-N-((1-((3,4-difluorophenyl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)methyl)benzamide; 4-methoxy-N-((1-((4-fluorophenyl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)methyl)benzamide; 2-chloro-6-fluoro-N-((1-((4-fluorophenyl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)methyl)benzamide; N-((1-((4-(2-(dimethylamino)ethoxy)phenyl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)methyl)-4-fluorobenzamide; 4-chloro-N-((1-((3,4-difluorophenyl)sulfonyl)-4-hydroxy-1,2,3,4-tetrahydroquinolin-7-yl)methyl)benzamide; N-((1-((4-fluorophenyl)sulfonyl)-3,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinolin-7-yl)methyl)-4-methoxybenzamide; 4-fluoro-N-((1-((4-fluorophenyl)sulfonyl)-2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)methyl)benzamide; 4-fluoro-N-((1-((4-hydroxyphenyl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)methyl)benzamide; 4-chloro-N-((3-((4-fluorophenyl)sulfonyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)benzamide; 4-chloro-N-((3-((3,4-difluorophenyl)sulfonyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)benzamide; 2-chloro-N-(1-((4-(2-(dimethylamino)ethoxy)phenyl)sulfonyl)-2-oxoindolin-6-yl)-6-fluorobenzamide; 2-chloro-6-fluoro-N-(1-((4-fluorophenyl)sulfonyl)-2-oxoindolin-6-yl)benzamide; or a pharmaceutically acceptable salt thereof.

[0141] Methods for preparing compounds described herein are illustrated in the following synthetic schemes. The schemes are given for the purpose of illustrating the invention, but not for limiting the scope or spirit of the invention. Starting materials shown in the schemes can be obtained from commercial sources or be prepared based on procedures described in the literature.

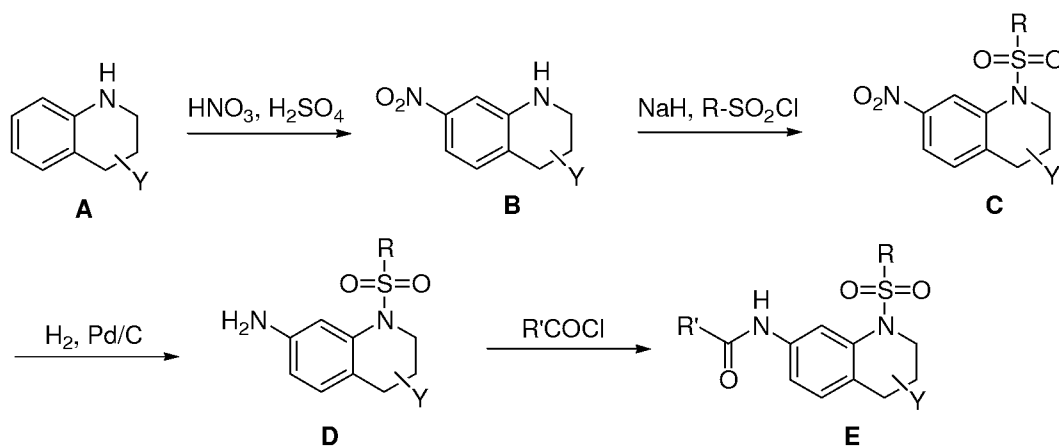
[0142] The synthetic route illustrated in Scheme 1 is a general method for preparing various amide-substituted tetrahydroquinoline compounds. Nitration of tetrahydroquinoline **A** by reacting it with a mixture of nitric acid and sulfuric acid provides 7-nitro-tetrahydroquinoline **B**. A sulfonamide group can be installed by reacting 7-nitro-tetrahydroquinoline **B** with a mild base and sulfonyl chloride (R-SO₂Cl) to provide sulfonamide **C**. The nitro group in compound **C** can be reduced to an amino group providing amino-tetrahydroquinoline **D**, which can be reacted with an acid chloride to provide the final amide-substituted tetrahydroquinoline **E**.

[0143] The reaction procedures in Scheme 1 are contemplated to be amenable to preparing a wide variety of amide-substituted tetrahydroquinoline compounds having different

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substituents at the Y, R, and R' positions. For example, a numerous substituted tetrahydroquinolines are known in the literature and/or are commercially available, such as 2-methyl tetrahydroquinoline, 3-methyl tetrahydroquinoline, 4-methyl tetrahydroquinoline, and 6-methyl tetrahydroquinoline. Furthermore, if a functional group that is part of the Y, R, or R' group would not be amenable to a reaction condition described in Scheme 1, it is contemplated that the functional group can first be protected using standard protecting group chemistry and strategies, and then the protecting group is removed after completing the desired synthetic transformation. See, for example, Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991, for further description of protecting chemistry and strategies. In certain other embodiments, a functional group in substituent Y, R, or R' in tetrahydroquinoline **E** can be converted to another functional group using standard functional group manipulation procedures known in the art. See, for example, "Comprehensive Organic Synthesis" (B.M. Trost & I. Fleming, eds., 1991-1992).

SCHEME 1.



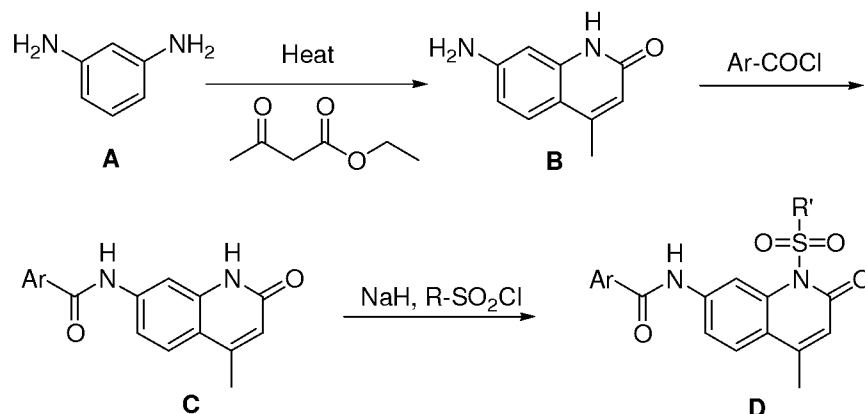
15

[0144] Scheme 2 illustrates a general method for preparing dihydroquinolines. Condensation of phenylene diamine **A** with ethyl acetoacetate under reflux (e.g., using Conrad-Limpach conditions) provides 7-amino-4-methylquinolin-2(1H)-one **B**. See, for example, *Med. Chem Res.* (2010) vol. 19, pages 193-209 for additional description of synthetic procedures. The amino group on quinolinone **B** can be reacted with an acid chloride to acylate the exocyclic nitrogen providing amide **C**. Reaction of amide **C** with mild base and a sulfonyl chloride ($\text{R}'\text{SO}_2\text{Cl}$) provides sulfonamido-dihydroquinoline **D**.

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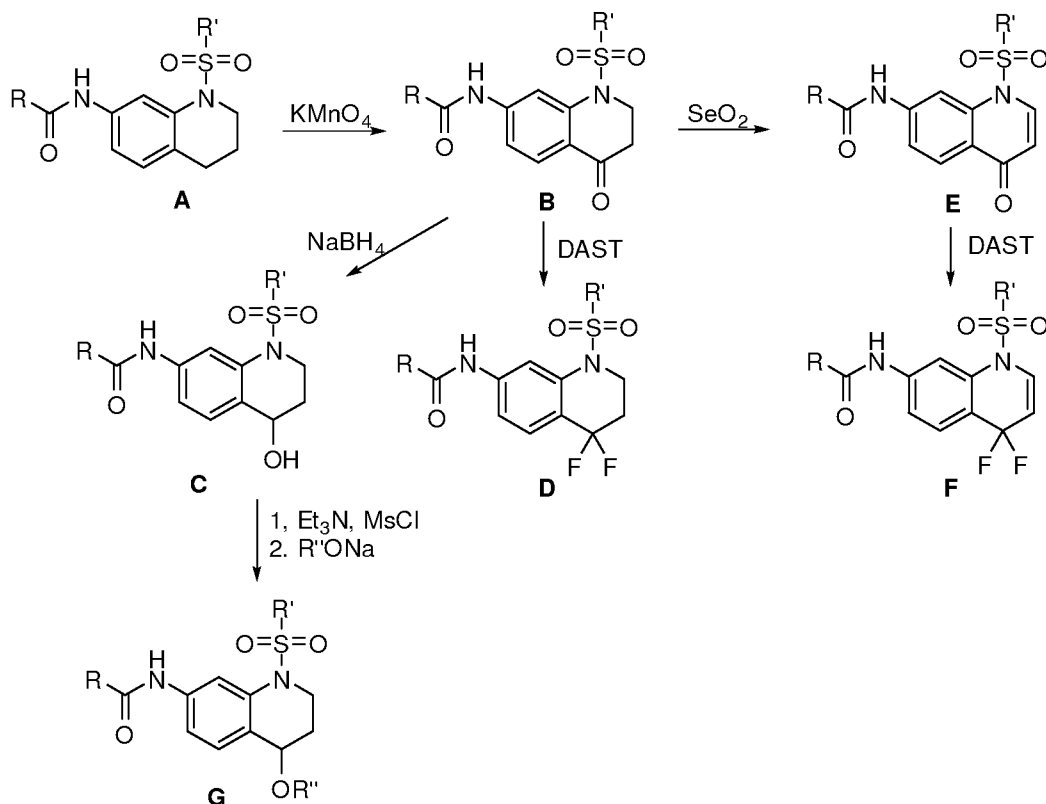
SCHEME 2.



[0145] Scheme 3 illustrates a general method for preparing fluoro-substituted, hydroxyl-
 5 substituted, and alkoxy-substituted tetrahydroquinoline compounds. Oxidation of
 tetrahydroquinoline **A** using potassium permanganate provides ketone **B**. Ketone **B** can
 be reduced to alcohol **C**, reacted with a fluorinating agent (such as DAST) to provide
 difluorotetrahydroquinoline **D**, or further oxidized to dihydroquinoline **E**. The oxidative
 conversion of ketone **B** to dihydroquinoline **E** can be carried using, for example, manganese
 10 dioxide, DDQ or selenium dioxide. Reaction of dihydroquinoline **E** with a fluorinating agent
 (such as DAST) provides fluoro-dihydroquinoline **F**. The identity of the oxidant and
 fluorinating agent can be selected to accommodate various functional groups that may be
 present on the synthetic intermediates shown in Scheme 3. Finally, as depicted below alkoxy-
 substituted tetrahydroquinoline **G** can be prepared by reaction of alcohol **C** with
 15 methanesulfonyl chloride to provide an intermediate mesylate that is reacted with an alkoxide,
 such as sodium methoxide, to provide alkoxy-substituted tetrahydroquinoline **G**.

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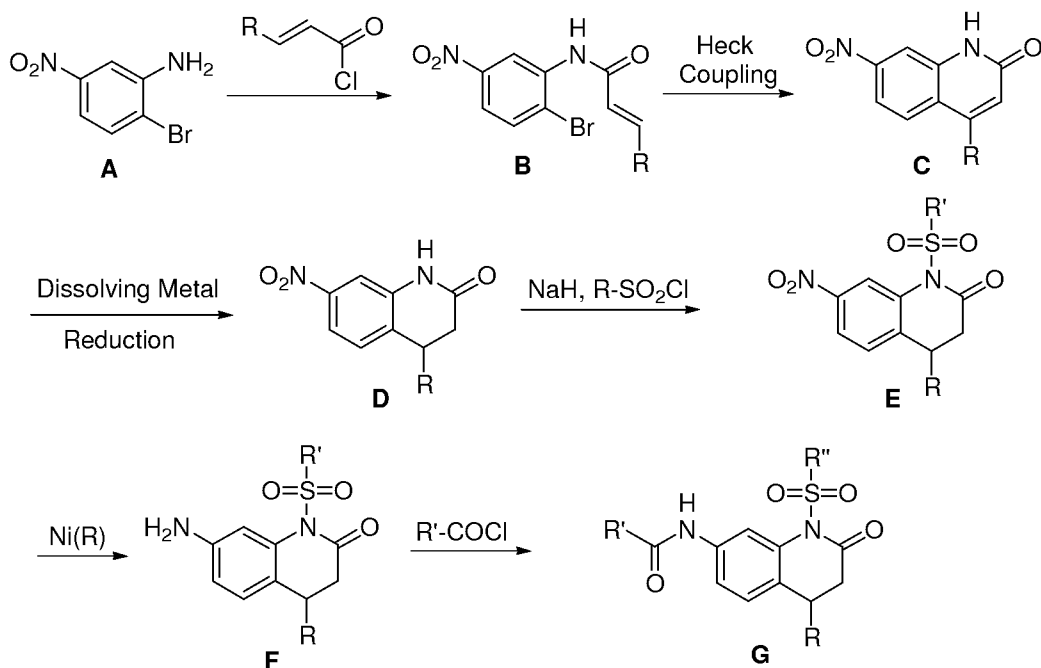
SCHEME 3.



- [0146] Scheme 4 illustrates a general method for preparing tetrahydroquinolines having, for example, a methyl group at the 4-position. Reaction of aniline **A** with an α,β -unsaturated acid chloride under Schotten-Baumen conditions (or using a solution of the acid chloride in a solvent such as pyridine, THF, or DMF with a nucleophilic catalyst and added organic base if appropriate) provides amide **B**. Intramolecular Heck reaction can be used to convert amide **B** to quinoline-2-one **C**. Selective reduction of the enamide double bond in compound **C** may be carried using a dissolving metal reduction, such as sodium in liquid ammonia or an aluminum-mercury amalgam, to provide dihydroquinolin-2-one **D**. Sulfonation of the amide nitrogen can be carried out by reacting dihydroquinolin-2-one **D** with a mild base and sulfonyl chloride (RSO_2Cl) to provide sulfamide **E**. Reduction of the nitro group in sulfonamide **E** can be carried out Raney nickel to provide amine **F**, which can be reacted with an acid chloride (or carboxylic acid under amide coupling conditions) to provide the desired bicyclopiperidone **G**.

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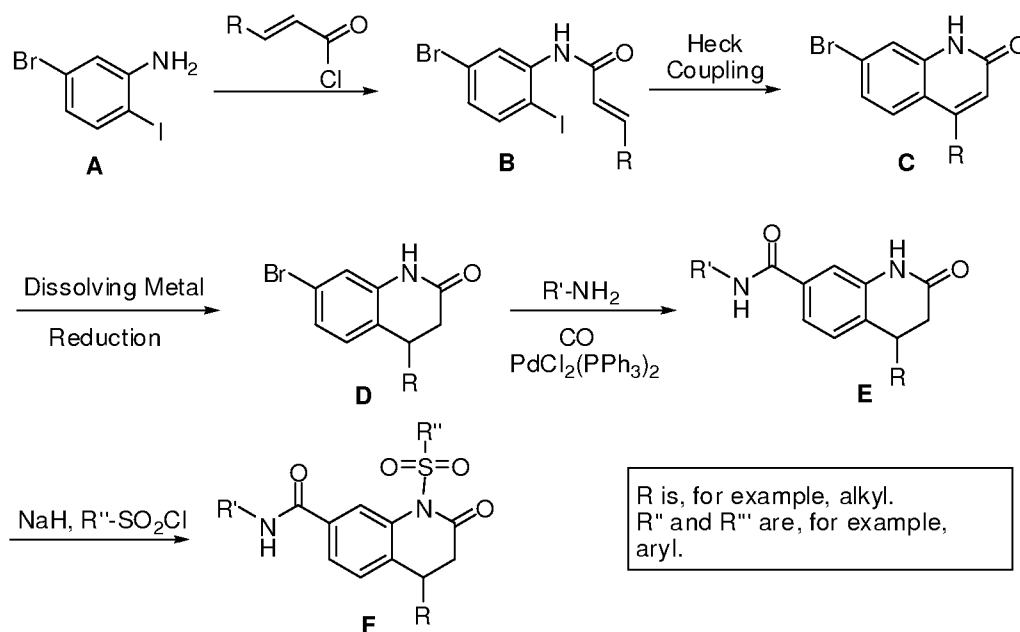
SCHEME 4.



- [0147]** Scheme 5 illustrates a general method for preparing tetrahydroquinolines having an amide substituent and, for example, and an alkyl substituent attached to the tetrahydroquinoline core. Amide coupling of halo-aniline **A** with an acid chloride provides amide **B**. Synthetic intermediate **B** is subjected to Heck Coupling conditions to provide bromoquinolin-2(1H)-one **C**, which can be reduced to bromo-dihydroquinolin-2(1H)-one **D**. Synthetic intermediate **D** can be converted to amide **E**, and subsequent reaction with the desired sulfonyl chloride provides the desired tetrahydroquinoline **F**.

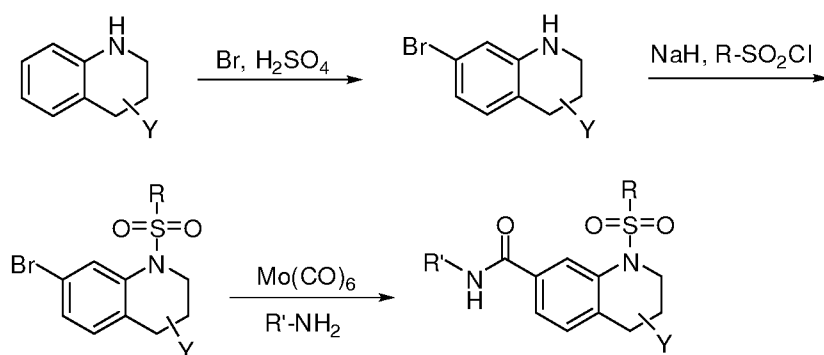
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SCHEME 5.



[0148] Scheme 6 illustrates an alternative procedure for preparing tetrahydroquinolines having an amide substituent and, for example, and an alkyl substituent attached to the tetrahydroquinoline core.

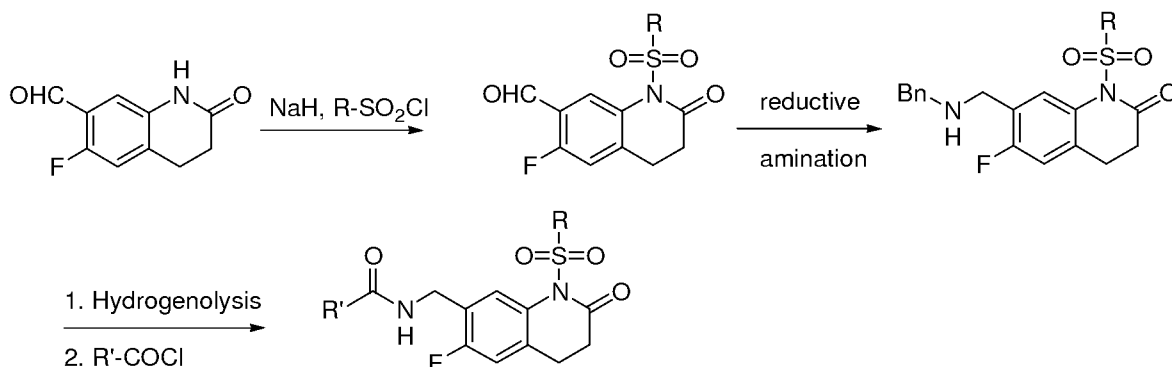
SCHEME 6.



[0149] Scheme 7 illustrates a general method for preparing fluorinated tetrahydroquinoline compounds. The starting tetrahydroquinoline-7-carbaldehyde compound shown in Scheme 7 has been described in the literature. See, for example, International Patent Application Publication WO 2010/038901.

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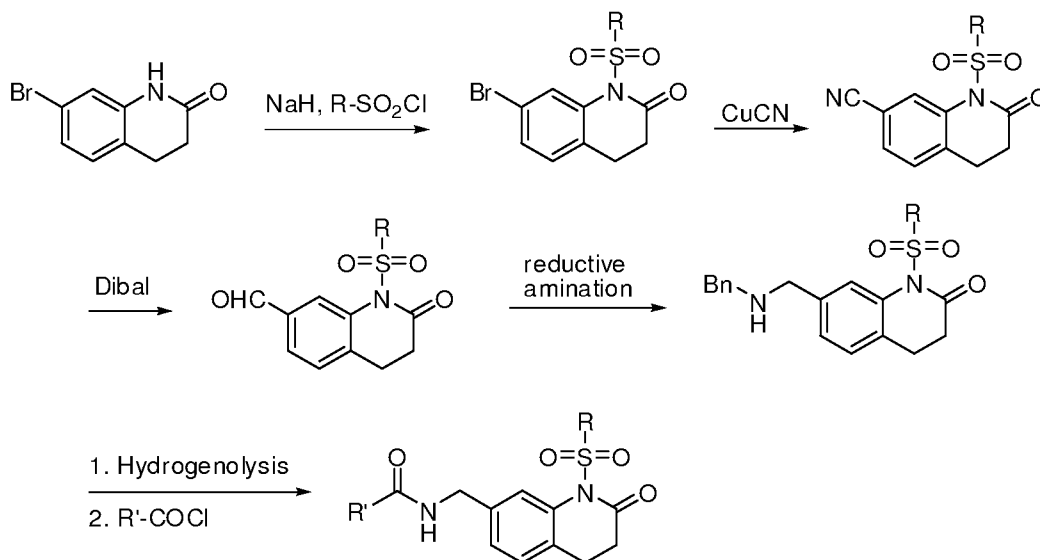
SCHEME 7.



- 5 [0150] Scheme 8 illustrates a general method for preparing tetrahydroquinoline compounds having a $-\text{CH}_2$ -amide substituent at the 7-position. Numerous indoles, indolinones, benzimidazoles, benzimidazolones and the like are known in the literature, and they are contemplated to be amenable for use as starting material in the synthetic scheme below to provide various functionalized 6,5-fused bicyclic ring systems.

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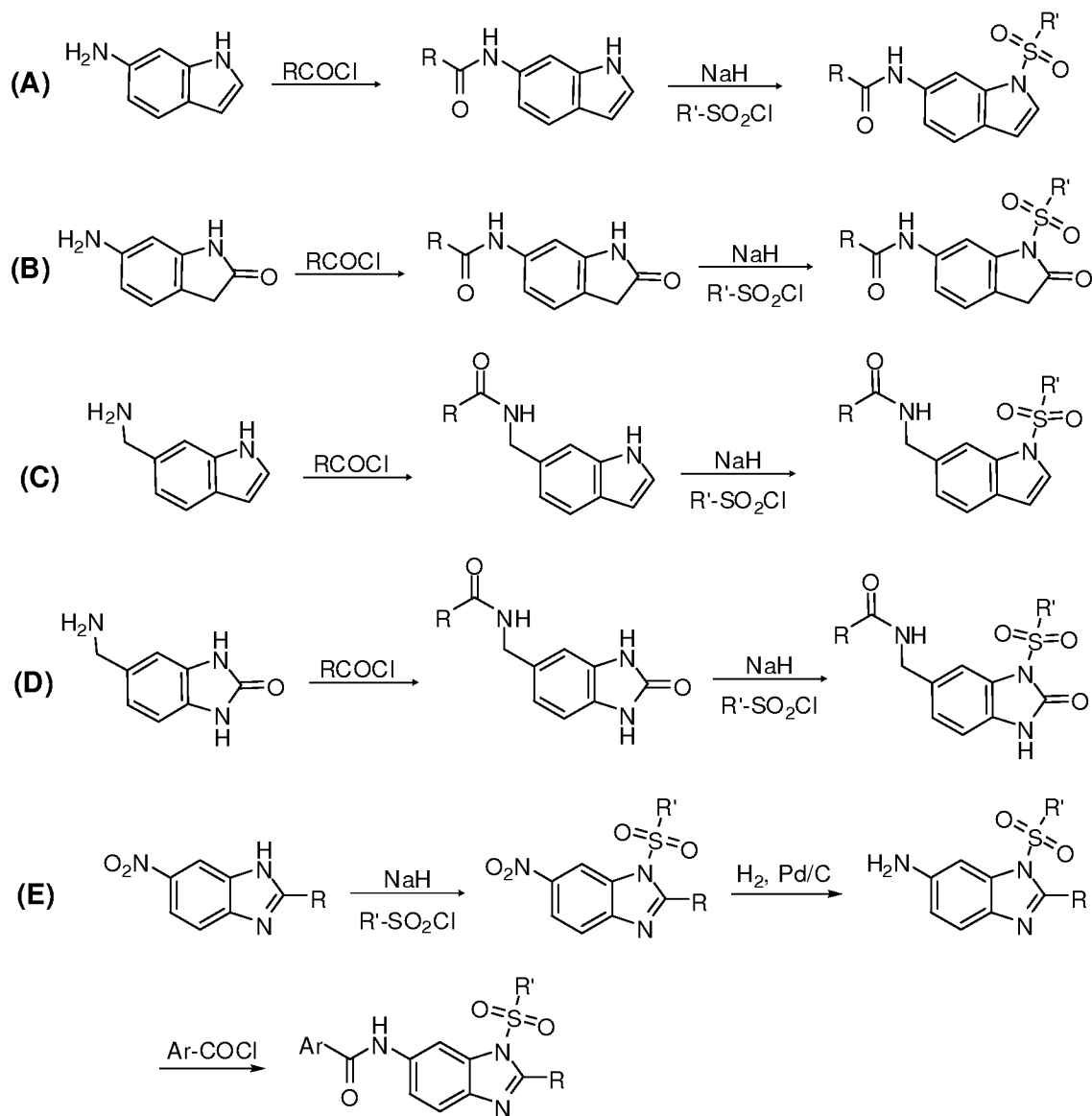
SCHEME 8.



- [0151] Scheme 9 illustrates multiple general procedures for preparing various indoles, indolinones and related compounds

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SCHEME 9.



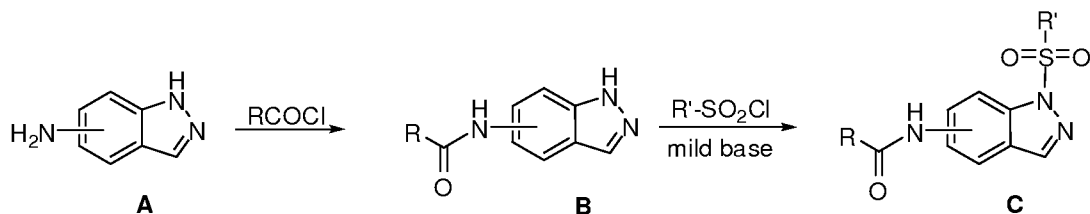
5

[0152] The synthetic route in Scheme 10 is a general method for preparing various amide-substituted indazole compounds. Reaction of amino-indazole **A** with an acid chloride (RC(O)Cl) provides amide-substituted indazole **B**. A sulfonamide group can be installed by reacting indazole **B** with a mild base and a sulfonyl chloride (R'-SO₂Cl) to provide indazolyl sulfonamide **C**.

10

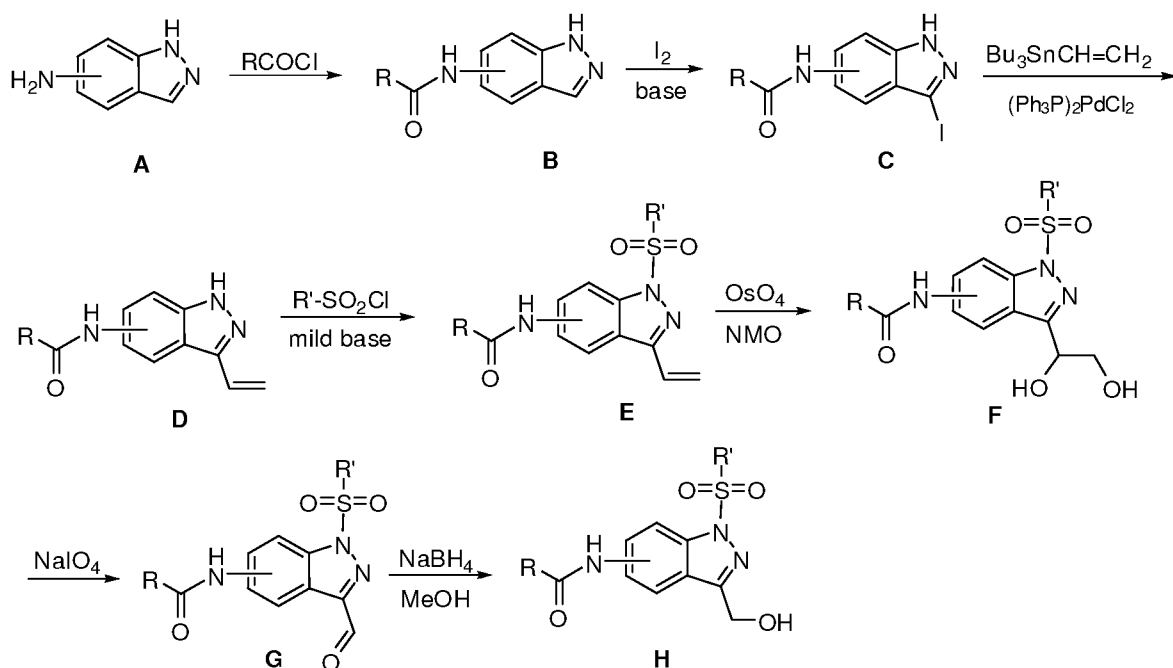
- 81 -

SCHEME 10



- [0153] The synthetic route in Scheme 11 is a general method for preparing various 3-substituted indazole compounds. Reaction of amino-indazole **A** with an acid chloride
- 5 (RC(O)Cl) provides amide-substituted indazole **B**. Treatment of indazole **B** with iodine provides iodo-indazole **C**, which may be subjected to palladium coupling conditions to provide 3-vinyl-imidazole **D**. A sulfonamide group can be installed by reacting 3-vinyl-imidazole **D**
- 10 with a mild base and a sulfonyl chloride (R'-SO₂Cl) to provide indazolyl sulfonamide **E**. Dihydroxylation of the vinyl group may be achieved by treating indazole **E** with osmium tetraoxide to provide dihydroxy-ethyl indazole **F**. Sodium periodate cleavage of the dihydroxy group produces aldehyde **G**, which may be reduced to provide 3-hydroxymethylindazole **H**.

SCHEME 11.

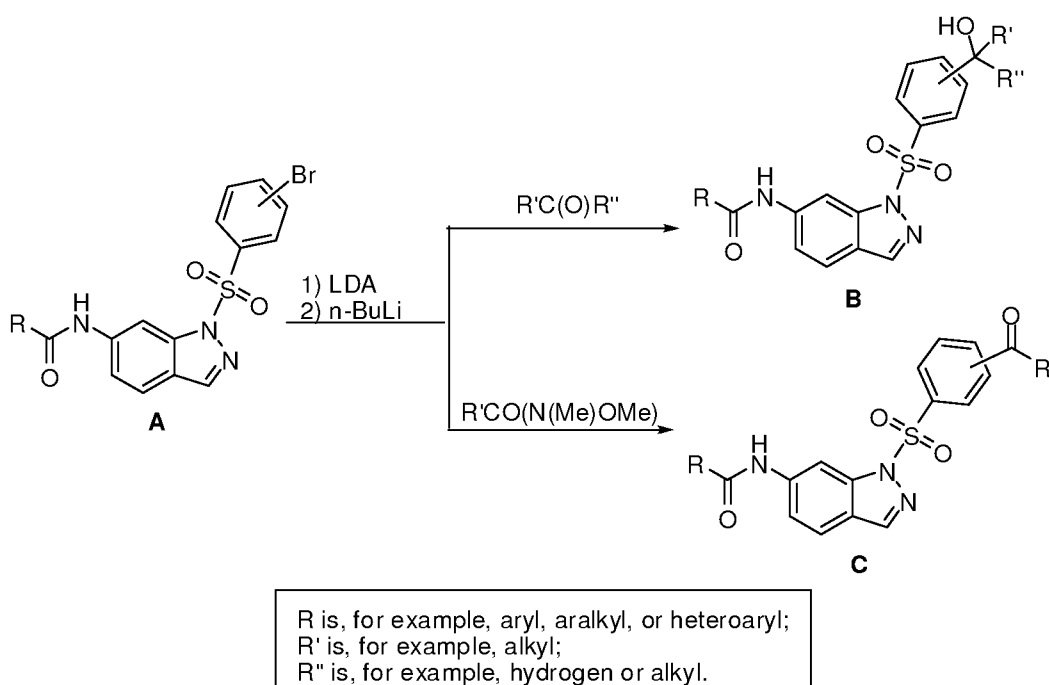


R and R' are, for example, aryl, aralkyl, or heteroaryl.

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[0154] Scheme 12 provides an alternative general method for preparing various amide-substituted indazole compounds. Treatment of bromo-phenylsulfonyl indazole **A** with lithium diisopropylamide (LDA), n-butyl lithium (n-BuLi), and a ketone or aldehyde ($R'C(O)R''$) provides indazole **B**. Treatment of bromo-phenylsulfonyl indazole **A** with lithium diisopropylamide (LDA), n-butyl lithium (n-BuLi), and the amide compound $R'C(O)N(Me)(OMe)$ provides indazole **C**.

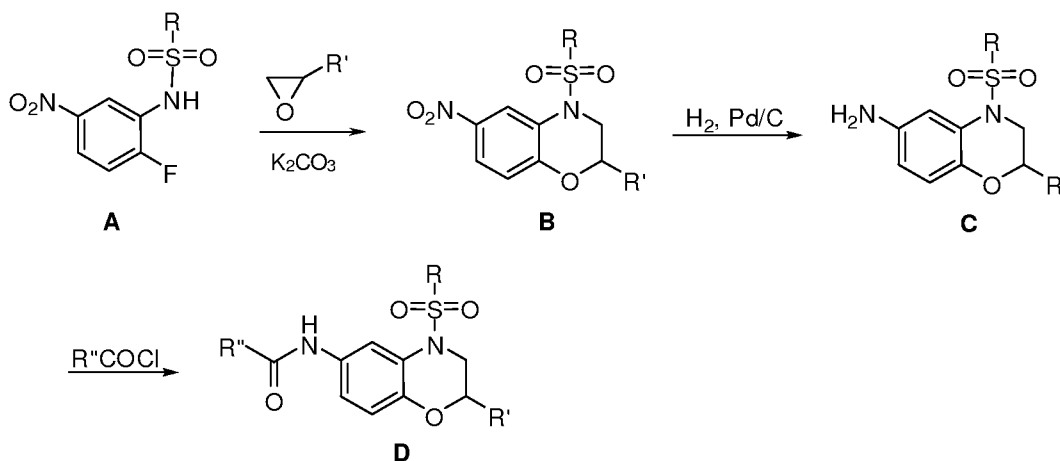
SCHEME 12.



[0155] The synthetic route in Scheme 13 is a general method for preparing various amide-substituted benzoxazine compounds. Reaction of nitro-aryl sulfonamide **A** with an epoxide provides benzoxazine **B**. The nitro group in benzoxazine **B** can be reduced to an amino group to provide amino-benzoxazine **C**. Reaction of amino-benzoxazine **C** with an acid chloride ($R''C(O)Cl$) provides amide-substituted benzoxazine **D**.

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SCHEME 13.

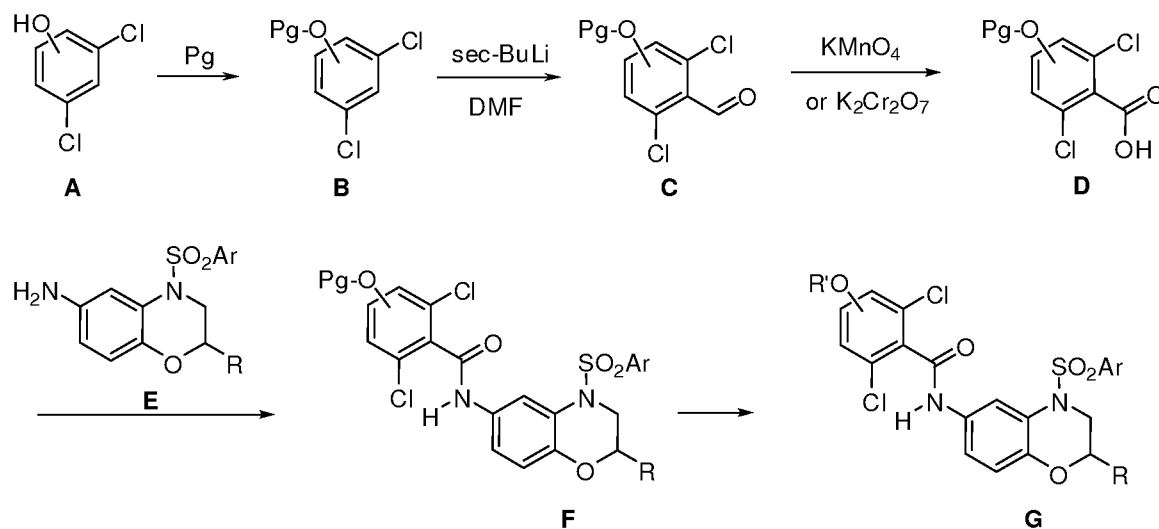


R and R' are, for example, aryl, aralkyl, or heteroaryl; and R' is, for example, alkyl.

- [0156]** Scheme 14 provides an alternative general method for preparing various amide-substituted benzoxazine compounds. Dichloro-hydroxybenzene **A** is reacted with a protecting group agent (e.g., tert-butyl-dimethylsilylchloride) to provide intermediate **B**, which can be treated with sec-butyl lithium (sec-BuLi) and dimethylformamide (DMF, an electrophilic formaldehyde source) to provide aldehyde **C**. Treatment of aldehyde **C** with an oxidizing agent (e.g., KMnO₄) provide substituted benzoic acid **D**. Amide coupling of substituted benzoic acid **D** and amino-benzoxazine **E** provides benzoxazine amide **F**. The protecting group (Pg) of benzoxazine amide **F** can be removed to provide hydroxy-benzamide **G**, which, if desired, can be converted to its alkyl ether (e.g., where R' is alkyl).

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SCHEME 14.

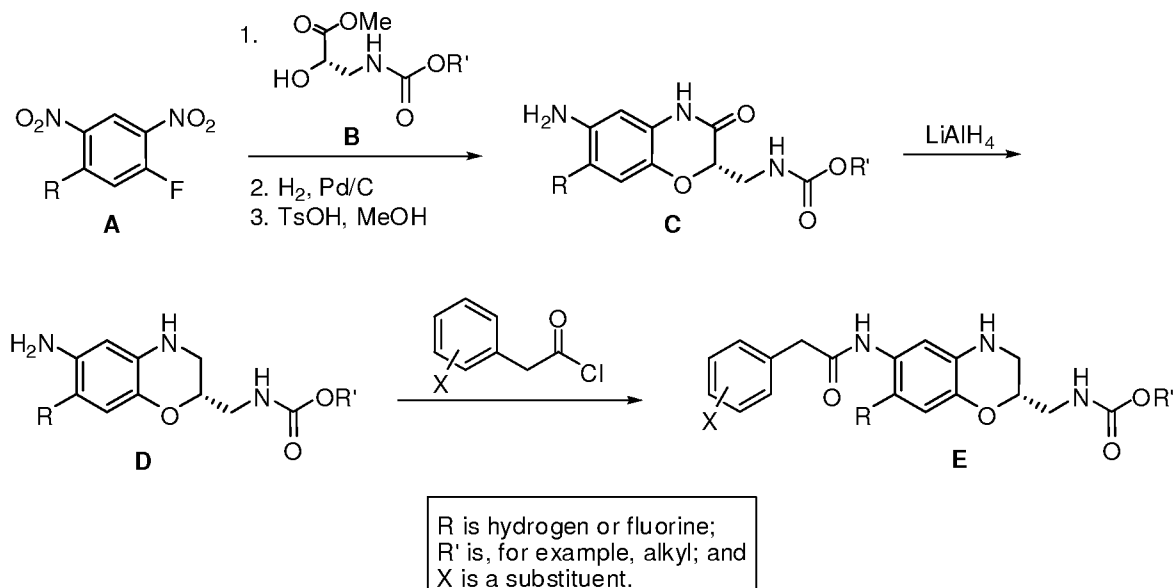


Pg is a protecting group;
 R is, for example, alkyl, hydroxyalkyl, aminoalkyl, alkylene-heterocyclic, heterocyclic, or alkylene-CO₂H; and
 R' is, for example, hydrogen, alkyl, or haloalkyl.

- [0157] Scheme 15 provides an alternative general method for preparing various amide-substituted benzoxazine compounds. Reaction of fluoro-dinitrobenzene **A** with α -hydroxyester **B** provides benzoxazinone **C**. The amide group in benzoxazinone **C** can be reduced using, for example, lithium aluminum hydride (LiAlH₄) to provide benzoxazine **D**. Amide coupling of benzoxazine **D** with an acid chloride provides amido-benzoxazine **E**.

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SCHEME 15.



- [0158]** Tetrahydroquinoline and related compounds described herein can be combined with a pharmaceutically acceptable carrier to form a pharmaceutical composition. For example, one aspect of the invention provides a pharmaceutical composition comprising (i) a pharmaceutically acceptable carrier and (ii) a compound represented by Formula V or VI, wherein Formula V and VI are as defined above. In certain other embodiments, the pharmaceutical composition comprises a compound of Formula V. In certain embodiments, the compound is one of the more specific embodiments specified above for Formula V, such as where A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, $-\text{N}(\text{R}^3)(\text{R}^4)$, $-\text{CN}$, $-\text{CO}_2\text{R}^6$, $-\text{C}(\text{O})-\text{C}_{1-6}$ alkyl, $-\text{C}_{1-6}$ alkylene- $\text{N}(\text{R}^3)(\text{R}^4)$, $-\text{C}_{1-6}$ alkylene- C_{1-6} alkoxy, $-\text{C}_{1-6}$ alkylene- CO_2R^6 , $-\text{O}-\text{C}_{1-6}$ alkylene- $\text{N}(\text{R}^3)(\text{R}^4)$, and $-\text{N}(\text{R}^6)\text{C}(\text{O})-\text{C}_{1-6}$ alkylene- $\text{N}(\text{R}^3)(\text{R}^4)$. In yet other embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen and C_{1-6} haloalkyl. In certain other embodiments, X is $-\text{C}(\text{R}^5)_2-\psi$, $-\text{C}(\text{R}^5)_2\text{C}(\text{R}^6)=\text{C}(\text{R}^6)-\psi$, $-\text{C}(\text{R}^6)=\text{C}(\text{R}^6)\text{C}(\text{R}^5)_2-\psi$, or $-\text{C}(\text{R}^6)=\text{C}(\text{R}^6)-\psi$. In certain other embodiments, X is $-\text{O}-\text{C}(\text{R}^6)_2-\psi$ or $-\text{O}-\text{C}(\text{R}^6)(\text{R}^9)\text{C}(\text{R}^6)_2-\psi$. In certain other embodiments, X is $-\text{C}(\text{R}^6)=\text{N}-\psi$ or $-\text{C}(\text{R}^{10})=\text{N}-\psi$. In certain other embodiments, X is $-(\text{CH}_2)_3-\psi$. In certain embodiments, R^2 is attached to the 7-position of the tetrahydroquinoline ring. In certain embodiments, R^2 is $-\text{N}(\text{R}^7)\text{C}(\text{O})\text{R}^8$. In certain embodiments, R^8 is aryl or aralkyl; each of

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which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, and -S-C₁₋₆alkyl. In certain other embodiments, R⁸ is aryl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl. In certain other embodiments, R⁸ is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl.

[0159] In certain other embodiments, the pharmaceutical composition comprises a compound of Formula V-A. In certain embodiments, the compound is one of the more specific embodiments specified above for Formula V-A, such as where A is aryl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CO₂R¹, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-CO₂R¹, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R¹)C(O)-C₁₋₆alkylene-N(R³)(R⁴). In certain embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen and C₁₋₆haloalkyl. In certain embodiments, A is phenyl substituted at the 4-position with fluorine or chlorine. In certain embodiments, X is -[C(R⁵)₂]_n-ψ, -C(R⁵)₂C(R⁶)=C(R⁸)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, or -C(R⁶)=C(R⁶)-ψ. In certain embodiments, X is -(CH₂)₃-ψ. In certain embodiments, X is -O-[C(R⁶)₂]_m-ψ, -N(R⁶)-[C(R⁶)₂]_m-ψ, -N=C(R⁶)-ψ, or -N=C(R⁶)C(R⁶)₂-ψ. In certain embodiments, R² is -N(R⁷)C(O)R⁸. In certain embodiments, R⁸ is aryl or aralkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, and -S-C₁₋₆alkyl.

[0160] In certain other embodiments, the pharmaceutical composition comprises a compound of Formula VI. In certain embodiments, the compound is one of the more specific embodiments specified above for Formula VI, such as where A is aryl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴). In certain other embodiments, A is phenyl substituted at the 4-position with fluorine or chlorine. In certain embodiments, R⁸ is phenyl substituted with 2 or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl.

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[0161] In certain other embodiments, the pharmaceutical composition comprises a compound of Formula VI-A. In certain embodiments, the compound is one of the more specific embodiments specified above for Formula VI-A, such as where A is aryl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CO₂R¹, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-CO₂R¹, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R¹)C(O)-C₁₋₆alkylene-N(R³)(R⁴). In certain embodiments, A is phenyl substituted at the 4-position with fluorine or chlorine. In certain embodiments, R⁸ is phenyl substituted with 2 or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, and -CN.

10 [0162] Another aspect of the invention provides the tetrahydroquinoline (and related compounds) described herein in the form of an isolated composition having a chemical purity of at least 95% w/w. In certain embodiments, the invention provides a compound of any one of Formulae I, II, III, or IV or a specific compound described herein (such as in Tables 1-6) in the form of an isolated composition having a chemical purity of at least 95% w/w, or at least 98%
15 w/w.

II. Therapeutic Applications of Tetrahydroquinoline and Related Compounds

[0163] It is contemplated that the tetrahydroquinoline and related compounds described herein, such as a compound of Formula I, II, III, IV, V, VI, VII, VIII, and IX provide therapeutic benefits to subjects suffering from an immune disorder or inflammatory disorder. Accordingly, one aspect of the invention provides a method of treating a disorder selected from the group consisting of an immune disorder or inflammatory disorder. The method comprises administering a therapeutically effective amount of a tetrahydroquinoline or related compound described herein, such as a compound of Formula I, II, III, IV, V, VI, VII, VIII, and IX, to a subject in need thereof to ameliorate a symptom of the disorder, wherein Formula I, II, III, IV, V, VI, VII, VIII, and IX are as described above. In certain embodiments, the particular
20 compound of Formula I, II, III, IV, V, VI, VII, VIII, and IX is the compound defined by one of the embodiments described above. In certain other embodiments, the tetrahydroquinoline or related compound described herein is a compound of Formula IX.

[0164] For example, in certain embodiments, the method comprises administering a
30 therapeutically effective amount of a compound of Formula IX (wherein Formula IX is as described in Section 1 above) to a subject in need thereof to ameliorate a symptom of the

disorder. In certain embodiments, the compound is a compound Formula IX, wherein A is aryl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂R⁶, -C(O)-C₁₋₆alkyl, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴). In certain other embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂R⁶, -C(O)-C₁₋₆alkyl, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴). In yet other embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, and -N(R³)(R⁴). In yet other embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, and -CN. In yet other embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen and C₁₋₆haloalkyl. In certain embodiments, X is -O-[C(R⁶)₂]_m-ψ or -O-[C(R⁶)(R⁹)C(R⁶)₂]-ψ. In certain other embodiments, X is -C(R⁶)=N-ψ or -C(R¹⁰)=N-ψ. In yet other embodiments, X is -C(R⁵)(C₁₋₆alkyl)[C(R⁵)₂]_m-ψ, -[C(R⁵)₂]_m-C(R⁵)(C₁₋₆alkyl)-ψ, -C(R⁵)₂-C(R⁵)(C₁₋₆alkyl)-C(R⁵)₂-ψ, -C(R⁵)₂C(R⁶)=C(R⁶)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, or -C(R⁶)=C(R⁶)-ψ. In certain embodiments, X is -(CH₂)₃-ψ. In certain embodiments, R² is attached to the 7-position of the tetrahydroquinoline ring. In certain embodiments, X is -C(O)-[C(R⁶)₂]_m-ψ. In certain embodiments, R² is -N(R⁷)C(O)R⁸. In certain embodiments, R⁸ is aryl or aralkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, and -S-C₁₋₆alkyl. In certain other embodiments, R⁸ is aryl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl. In yet other embodiments, R⁸ is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl. In certain embodiments, R⁸ is phenyl substituted with 2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl, where the first substituent is located at the 2-position of the phenyl group, and the second substituent is located at the 6-position of the phenyl group. In certain embodiments, y is 1.

[0165] In certain other embodiments, the tetrahydroquinoline or related compound described herein used in the method is a compound of Formula IX-A. In certain embodiments, the compound is a compound of Formula IX-A where A is aryl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CO₂R¹, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-CO₂R¹, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R¹)C(O)-C₁₋₆alkylene-N(R³)(R⁴). In certain embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, and -N(R³)(R⁴). In certain embodiments, A is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen and C₁₋₆haloalkyl. In certain embodiments, X -[C(R⁵)₂]_n-ψ, -C(R⁵)₂C(R⁶)=C(R⁸)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, or -C(R⁶)=C(R⁶)-ψ. In certain embodiments, X is -(CH₂)₃-ψ. In certain embodiments, X is -O-[C(R⁶)₂]_m-ψ, -N(R⁶)-[C(R⁶)₂]_m-ψ, -N=C(R⁶)-ψ, or -N=C(R⁶)C(R⁶)₂-ψ. In certain embodiments, R² is -N(R⁷)C(O)R⁸. In certain embodiments, R² is -(C₁₋₂alkylene)-N(R⁷)C(O)R⁸ or -C(O)N(R⁷)(R⁸). In certain embodiments, R² is a heteroaryl group optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, and -N(R³)(R⁴). In certain embodiments, R⁸ is aryl or aralkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, and -S-C₁₋₆alkyl. In certain embodiments, R⁸ is aryl or aralkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, and -CO₂-C₁₋₆alkyl. In certain embodiments, R⁸ is an aromatic heterocyclyl or -C(R⁶)₂-(aromatic heterocyclyl); each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆alkyl, and -S-C₁₋₆alkyl.

[0166] In certain embodiments, the disorder an immune disorder. In certain other embodiments, the disorder is an inflammatory disorder. In certain other embodiments, the disorder is an autoimmune disorder. In certain other embodiments, the disorder is rheumatoid arthritis, psoriasis, chronic graft-versus-host disease, acute graft-versus-host disease, Crohn's disease, inflammatory bowel disease, multiple sclerosis, systemic lupus erythematosus, Celiac

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Sprue, idiopathic thrombocytopenic thrombotic purpura, myasthenia gravis, Sjogren's syndrome, scleroderma, ulcerative colitis, asthma, or epidermal hyperplasia.

[0167] In certain other embodiments, the disorder is cartilage inflammation, bone degradation, arthritis, juvenile arthritis, juvenile rheumatoid arthritis, pauciarticular juvenile
5 rheumatoid arthritis, polyarticular juvenile rheumatoid arthritis, systemic onset juvenile rheumatoid arthritis, juvenile ankylosing spondylitis, juvenile enteropathic arthritis, juvenile reactive arthritis, juvenile Reter's Syndrome, SEA Syndrome, juvenile dermatomyositis, juvenile psoriatic arthritis, juvenile scleroderma, juvenile systemic lupus erythematosus, juvenile vasculitis, pauciarticular rheumatoid arthritis, polyarticular rheumatoid arthritis,
10 systemic onset rheumatoid arthritis, ankylosing spondylitis, enteropathic arthritis, reactive arthritis, Reter's Syndrome, dermatomyositis, psoriatic arthritis, vasculitis, myolitis, polymyolitis, dermatomyolitis, osteoarthritis, polyarteritis nodosa, Wegener's granulomatosis, arteritis, polymyalgia rheumatica, sarcoidosis, sclerosis, primary biliary sclerosis, sclerosing cholangitis, dermatitis, atopic dermatitis, atherosclerosis, Still's disease, chronic obstructive
15 pulmonary disease, Guillain-Barre disease, Type I diabetes mellitus, Graves' disease, Addison's disease, Raynaud's phenomenon, autoimmune hepatitis, psoriatic epidermal hyperplasia, plaque psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, erythrodermic psoriasis, or an immune disorder associated with or arising from activity of pathogenic lymphocytes. In certain embodiments, the psoriasis is plaque psoriasis, guttate psoriasis, inverse psoriasis, pustular
20 psoriasis, or erythrodermic psoriasis.

[0168] In certain other embodiments, the disorder is rheumatoid arthritis.

[0169] In certain embodiments, the subject is a human. In certain embodiments, the compound is a compound of Formula IX-A, IX-B, or IX-C.

[0170] Another aspect of the invention provides for the use of a compound described herein
25 (such as a compound of Formula I, II, III, IV, V, VI, VII, VIII, or IX) in the manufacture of a medicament. In certain embodiments, the medicament is for treating a disorder described herein, such as rheumatoid arthritis.

[0171] Another aspect of the invention provides for the use of a compound described herein
30 (such as a compound of Formula I, II, III, IV, V, VI, VII, VIII, or IX) for treating a medical disorder, such a medical disorder described herein (e.g., rheumatoid arthritis).

[0172] Further, it is contemplated that tetrahydroquinoline and related compounds described herein, such as a compound of Formula I, II, III, IV, V, VI, VII, VIII, or IX, can inhibit the activity of ROR γ . Accordingly, another aspect of the invention provides a method of inhibiting the activity of ROR γ . The method comprises exposing a ROR γ to an effective
5 amount of a tetrahydroquinoline or related compound described herein, such as a compound of Formula I, II, III, IV, V, VI, VII, VIII, or IX, to inhibit said ROR γ , wherein Formula I, II, III, IV, V, VI, VII, VIII, or IX are as described above. In certain embodiments, the particular compound of Formula I, II, III, IV, V, VI, VII, VIII, or IX is the compound defined by one of the embodiments described above. In certain embodiments, the tetrahydroquinoline or related
10 compound is a compound of Formula I, II, III, IV, V, VI, VII, or VIII.

[0173] Further, it is contemplated that tetrahydroquinoline and related compounds described herein, such as a compound of Formula I, II, III, IV, V, VI, VII, VIII, and IX, can reduce the amount of interleukin-17 (IL-17) in a subject. IL-17 is a cytokine that affects numerous biological functions, including inducing and mediating pro-inflammatory responses.
15 Accordingly, another aspect of the invention provides a method of reducing the amount of IL-17 in a subject. The method comprises administering to a subject an effective amount of a tetrahydroquinoline or related compound described herein, such as a compound of I, II, III, IV, V, VI, VII, VIII, or IX to reduce the amount of IL-17 in the subject, wherein Formula I, II, III, IV, V, VI, VII, VIII, or IX are as described above. In certain embodiments, the particular
20 compound of Formula I, II, III, IV, V, VI, VII, VIII, or IX is the compound defined by one of the embodiments described above. In certain embodiments, the tetrahydroquinoline or related compound is a compound of Formula I, II, III, IV, V, VI, VII, or VIII.

[0174] In certain embodiments, the subject is a human. In certain embodiments, administering the compound reduces the amount of IL-17 produced by Th-17 cells in the
25 subject. A change in the amount of IL-17 produced by, for example, Th-17 cells can be measured using procedures described in the literature, such as an ELISA assay or intracellular staining assay.

[0175] Further, it is contemplated that tetrahydroquinoline and related compounds described herein, such as a compound of Formula I, II, III, IV, V, VI, VII, VIII, and IX, may
30 inhibit the synthesis of IL-17 in a subject. Accordingly, another aspect of the invention provides a method of inhibiting the synthesis IL-17 in a subject. The method comprises administering to a subject an effective amount of a compound described herein, e.g., a

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compound of Formula I, II, III, IV, V, VI, VII, VIII, and IX, to inhibit the synthesis IL-17 in the subject, wherein Formula I, II, III, IV, V, VI, VII, VIII, and IX are as described above. In certain embodiments, the particular compound of Formula I, II, III, IV, V, VI, VII, VIII, and IX is the compound defined by one of the embodiments described above. In certain embodiments, the tetrahydroquinoline or related compound is a compound of Formula I, II, III, IV, V, VI, VII, or VIII.

[0176] The description above describes multiple embodiments providing definitions for variables used herein. The application specifically contemplates all combinations of such variables, e.g., particular combinations of the definitions set forth for variables A and X.

10 III. Combination Therapy

[0177] Another aspect of the invention provides for combination therapy. Tetrahydroquinoline and related compounds (e.g., a compound of Formula I, II, III, IV, V, VI, VII, VIII, or IX) or their pharmaceutically acceptable salts may be used in combination with additional therapeutic agents to treat medical disorders, such as medical disorders associated with inappropriate IL-17 pathway activity. Exemplary additional therapeutic agents include, for example, (1) a TNF- α inhibitor; (2) a non-selective COX-1/COX-2 inhibitor; (3) a selective COX-2 inhibitor, such as celecoxib and rofecoxib; (4) other agents for treating inflammatory disease and autoimmune disease including, for example, methotrexate, leflunomide, sulfasalazine, azathioprine, penicillamine, bucillamine, actarit, mizoribine, lobenzarit, hydroxychloroquine, d-penicillamine, aurothiomalate, auranofin, parenteral gold, oral gold, cyclophosphamide, Lymphostat-B, a BAFF/APRIL inhibitor, CTLA-4-Ig, or a mimetic of CTLA-4-Ig; (5) a leukotriene biosynthesis inhibitor, such as a 5-lipoxygenase (5-LO) inhibitor, or a 5-lipoxygenase activating protein (FLAP) antagonist; (6) a LTD4 receptor antagonist; (7) a phosphodiesterase type IV (PDE-IV) inhibitor, such as cilomilast (ariflo) or roflumilast; (8) an antihistamine H1 receptor antagonist; (9) an α 1- and α 2-adrenoceptor agonist; (10) an anticholinergic agent; (11) a β -adrenoceptor agonist; (12) an insulin-like growth factor type I (IGF-1) mimetic; (13) a glucocorticoid; (14) a kinase inhibitor such as an inhibitor of a Janus Kinase (e.g., JAK 1 and/or JAK2 and/or JAK 3 and/or TYK2), p38 MAPK, Syk or IKK2; (15) a B-cell target biologic such as rituximab; (16) a selective co-stimulation modulator such as abatacept; (17) an interleukin inhibitor or interleukin receptor inhibitor, such as the IL-1 inhibitor anakinra, IL-6 inhibitor tocilizumab, and IL12/IL-23 inhibitor ustekimumab; (18) an anti-IL17 antibody, anti-IL21 antibody, or anti-IL22 antibody (19) a S1P1 agonist, such as

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fingolimod; (20) an interferon, such as interferon beta 1; (21) an integrin inhibitor such as natalizumab; (22) a mTOR inhibitor such as rapamycin, cyclosporin and tacrolimus; (23) a non-steroidal antiinflammatory agent (NSAID), such as propionic acid derivatives (alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, 5 flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, piroprofen, pranoprofen, suprofen, tiaprofenic acid, and tioxaprofen), acetic acid derivatives (indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac), fenamic acid derivatives (flufenamic acid, meclofenamic acid, mefenamic acid, 10 niflumic acid and tolfenamic acid), biphenylcarboxylic acid derivatives (diflunisal and flufenisal), oxicams (isoxicam, piroxicam, sudoxicam and tenoxicam), salicylates (acetyl salicylic acid, sulfasalazine) and pyrazolones (apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone); (24) a NRF2 pathway activator, such as the fumaric acid derivative, BG-12; and (25) a chemokine or chemokine receptor inhibitor, such as 15 a CCR9 antagonist.

[0178] The amount tetrahydroquinoline or related compound (e.g., a compound of Formula I, II, III, IV, V, VI, VII, VIII, or IX) and additional therapeutic agent and the relative timing of administration may be selected in order to achieve a desired combined therapeutic effect. For example, when administering a combination therapy to a patient in need of such administration, 20 the therapeutic agents in the combination, or a pharmaceutical composition or compositions comprising the therapeutic agents, may be administered in any order such as, for example, sequentially, concurrently, together, simultaneously and the like. Further, for example, a tetrahydroquinoline or related compound (e.g., a compound of any one of formulae I-IX) may be administered during a time when the additional therapeutic agent(s) exerts its prophylactic 25 or therapeutic effect, or *vice versa*.

[0179] The doses and dosage regimen of the active ingredients used in the combination therapy may be determined by an attending clinician. In certain embodiments, the tetrahydroquinoline or related compound (e.g., a compound of any one of formulae I-IX) and the additional therapeutic agent(s) are administered in doses commonly employed when such 30 agents are used as monotherapy for treating the disorder. In other embodiments, the tetrahydroquinoline or related compound (e.g., a compound of any one of formulae I-IX) and the additional therapeutic agent(s) are administered in doses lower than the doses commonly

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employed when such agents are used as monotherapy for treating the disorder. In certain embodiments, the tetrahydroquinoline or related compound (e.g., a compound of any one of formulae I-IX) and the additional therapeutic agent(s) are present in the same composition, which is suitable for oral administration.

5 [0180] In certain embodiments, the tetrahydroquinoline or related compound (e.g., a compound of any one of formulae I-IX) and the additional therapeutic agent(s) may act additively or synergistically. A synergistic combination may allow the use of lower dosages of one or more agents and/or less frequent administration of one or more agents of a combination therapy. A lower dosage or less frequent administration of one or more agents may lower
10 toxicity of the therapy without reducing the efficacy of the therapy.

[0181] Another aspect of this invention is a kit comprising a therapeutically effective amount of the tetrahydroquinoline or related compound (e.g., a compound of any one of formulae I-IX), a pharmaceutically acceptable carrier, vehicle or diluent, and optionally at least one additional therapeutic agent listed above.

15 IV. Pharmaceutical Compositions and Dosing Considerations

[0182] As indicated above, the invention provides pharmaceutical compositions, which comprise a therapeutically-effective amount of one or more of the compounds described above, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents. The pharmaceutical compositions may be specially formulated for administration in
20 solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, e.g., those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or
25 suspension, or sustained-release formulation; (3) topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin; (4) intravaginally or intrarectally, for example, as a pessary, cream or foam; (5) sublingually; (6) ocularly; (7) transdermally; or (8) nasally.

[0183] The phrase "therapeutically-effective amount" as used herein means that amount of
30 a compound, material, or composition comprising a compound of the present invention which

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is effective for producing some desired therapeutic effect in at least a sub-population of cells in an animal at a reasonable benefit/risk ratio applicable to any medical treatment.

[0184] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound
5 medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0185] Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening,
10 flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

[0186] Examples of pharmaceutically-acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl
15 palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

[0187] Formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The
20 formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally
25 be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred per cent, this amount will range from about 0.1 per cent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

[0188] In certain embodiments, a formulation of the present invention comprises an
30 excipient selected from the group consisting of cyclodextrins, celluloses, liposomes, micelle forming agents, e.g., bile acids, and polymeric carriers, e.g., polyesters and polyanhydrides; and

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a compound of the present invention. In certain embodiments, an aforementioned formulation renders orally bioavailable a compound of the present invention.

[0189] Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[0190] Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

[0191] In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules, trouches and the like), the active ingredient is mixed with one or more pharmaceutically-acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds and surfactants, such as poloxamer and sodium lauryl sulfate; (7) wetting agents, such as, for example, cetyl alcohol, glycerol monostearate, and non-ionic surfactants; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, zinc stearate, sodium stearate, stearic acid, and mixtures thereof; (10) coloring agents; and (11) controlled release agents such as crospovidone or ethyl cellulose. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may

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also be employed as fillers in soft and hard-shelled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[0192] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin
5 or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[0193] The tablets, and other solid dosage forms of the pharmaceutical compositions of the
10 present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices,
15 liposomes and/or microspheres. They may be formulated for rapid release, e.g., freeze-dried. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that
20 they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

[0194] Liquid dosage forms for oral administration of the compounds of the invention
25 include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular,
30 cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

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[0195] Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

5 [0196] Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

10 [0197] Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

15 [0198] Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

20 [0199] Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically-acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

25 [0200] The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[0201] Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

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[0202] Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by
5 either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

[0203] Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

[0204] Pharmaceutical compositions of this invention suitable for parenteral administration
10 comprise one or more compounds of the invention in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain sugars, alcohols, antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the
15 intended recipient or suspending or thickening agents.

[0205] Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper
20 fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0206] These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms
25 upon the subject compounds may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum
30 monostearate and gelatin.

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[0207] In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of
5 dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[0208] Injectable depot forms are made by forming microencapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the
10 ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

[0209] When the compounds of the present invention are administered as pharmaceuticals,
15 to humans and animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99% (more preferably, 10 to 30%) of active ingredient in combination with a pharmaceutically acceptable carrier.

[0210] The preparations of the present invention may be given orally, parenterally, topically, or rectally. They are of course given in forms suitable for each administration route.
20 For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, etc. administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. Oral administrations are preferred.

[0211] The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by
25 injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticulare, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

[0212] The phrases "systemic administration," "administered systemically," "peripheral
30 administration" and "administered peripherally" as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that

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it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

[0213] These compounds may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray,
5 rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually.

[0214] Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically-acceptable dosage
10 forms by conventional methods known to those of skill in the art.

[0215] Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

[0216] The selected dosage level will depend upon a variety of factors including the
15 activity of the particular compound of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the rate and extent of absorption, the duration of the treatment, other drugs, compounds and/or materials used in combination with
20 the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

[0217] A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in
25 the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

[0218] In general, a suitable daily dose of a compound of the invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Preferably, the
30 compounds are administered at about 0.01 mg/kg to about 200 mg/kg, more preferably at about 0.1 mg/kg to about 100 mg/kg, even more preferably at about 0.5 mg/kg to about 50 mg/kg.

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When the compounds described herein are co-administered with another agent (*e.g.*, as sensitizing agents), the effective amount may be less than when the agent is used alone.

[0219] If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals
5 throughout the day, optionally, in unit dosage forms. Preferred dosing is one administration per day.

[0220] The invention further provides a unit dosage form (such as a tablet or capsule) comprising a tetrahydroquinoline or related compound described herein (such as a compound of any one of Formulae I-IX or a specific compound described herein, such as in Tables 1-6) in
10 a therapeutically effective amount for the treatment of an immune or inflammatory disorder, such as one of the particular immune disorders or inflammatory disorders described herein.

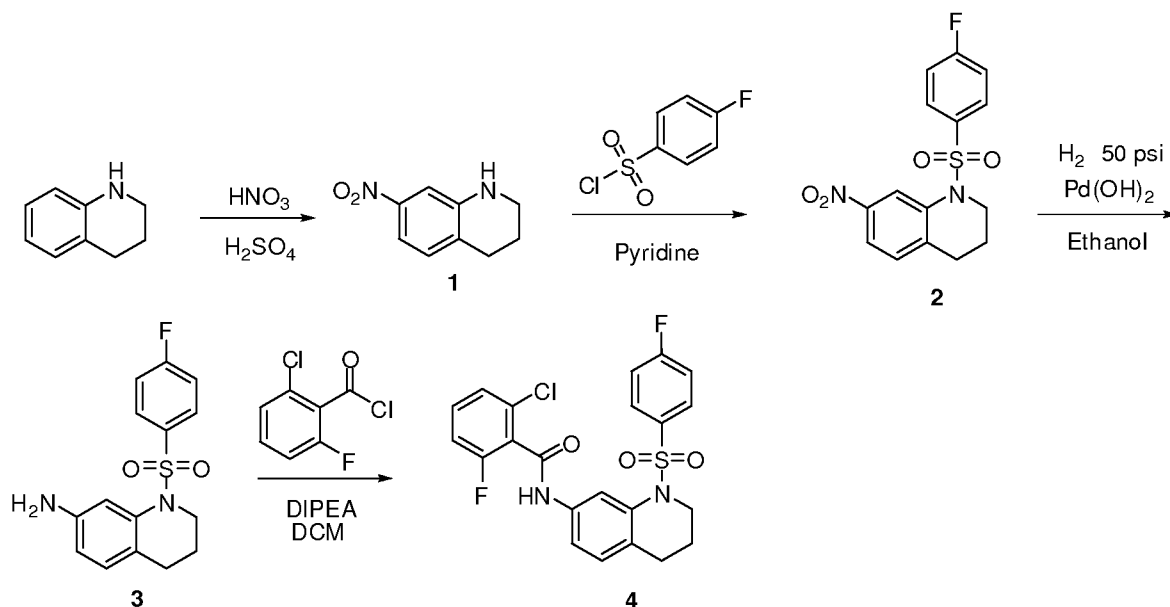
EXAMPLES

[0221] The invention now being generally described, will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the
15 invention.

EXAMPLE 1 – Synthesis of 2-Chloro-6-fluoro-N-[1-(4-fluoro-benzenesulfonyl)-1,2,3,4-tetrahydro-quinolin-7-yl]-benzamide (4)

[0222] The title compound was prepared according to the synthetic procedures described in the following scheme and Parts I-III below.

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[0223] Part I -- Synthesis of 1,2,3,4-Tetrahydro-7-nitroquinoline (1): 1,2,3,4-

Tetrahydroquinoline (26.8 g, 0.2 mol) was dissolved in 75 mL of 96.6% sulfuric acid and cooled in a salt-ice bath to -10°C . After stirring for 30 min, 9.5 mL (0.2 mol) of 90% nitric acid in 40 mL of sulfuric acid was added at such a rate that the temperature remained at -5 to -10°C . The reaction mixture was stirred in the ice bath for 3 hr and then poured onto ice. The solution was neutralized to pH 8 with sodium carbonate and the precipitate was filtered, washed with water, and dried to provide the title compound in crude form, which was purified by column chromatography using a hexanes:ethyl acetate gradient (0-30%) to provide the title compound in pure form as an orange solid (21.4 g, 59% yield).

[0224] Part II -- Synthesis of 1-(4-Fluoro-benzenesulfonyl)-7-nitro-1,2,3,4-tetrahydro-

quinoline (2): Into a 250 mL sealed reaction vessel was combined 1,2,3,4-tetrahydro-7-nitroquinoline (3 g, 0.017 mol), 4-fluorobenzene-1-sulfonyl chloride (6.61 g, 0.034 mol), and pyridine (15 mL). The mixture was heated at 80°C for two hours, cooled, and water (100 mL) was added to provide a mixture. This mixture was extracted with dichloromethane (DCM) (3 x 20 mL) and the combined extracts were washed with water (3 x 20 mL), dried over sodium sulfate, and the solvent was removed *in vacuo* to yield the title compound in crude form, which was purified by column chromatography using a hexanes:ethyl acetate gradient (5-20%) to provide the title compound in pure form as a yellow solid (3.12 g, 55% yield).

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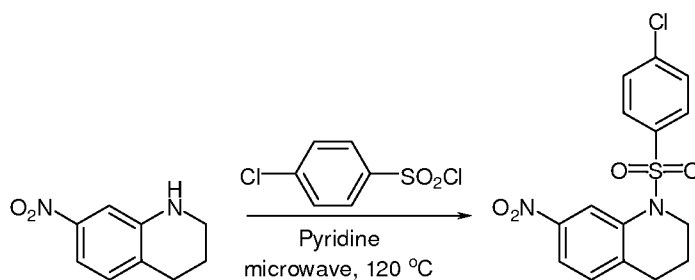
[0225] **Part III -- Synthesis of 1-(4-Fluoro-benzenesulfonyl)-1,2,3,4-tetrahydro-quinolin-7-ylamine (3):** Into a pressure vessel was combined 1-(4-fluoro-benzenesulfonyl)-7-nitro-1,2,3,4-tetrahydro-quinoline (2.4 g, 0.007 mol), ethanol (10 mL) and dichloroethane (5 mL). A catalytic amount of palladium hydroxide (~100 mg) was added to the pressure vessel, and then the vessel was filled with hydrogen and evacuated three times. Next, the vessel was pressurized to 50 psi with hydrogen and agitated for 1.5 hours, after which the mixture was filtered over celite and concentrated to yield the title compound as an off white solid (1.97 g, 92% yield) (M+H =307.3).

[0226] **Part IV -- Synthesis of 2-Chloro-6-fluoro-N-[1-(4-fluoro-benzenesulfonyl)-1,2,3,4-tetrahydro-quinolin-7-yl]-benzamide (4):** Into a 20 mL reaction vessel was combined 1-(4-fluoro-benzenesulfonyl)-1,2,3,4-tetrahydro-quinolin-7-ylamine (0.1 g, 0.3 mmol), dichloromethane (1 mL) and *N,N*-diisopropylethylamine (0.078 g, 0.6 mmol). The compound 2-chloro-6-fluorobenzoyl chloride (0.064 g, 0.33 mmol) was added dropwise to the reaction vessel. The resultant mixture was allowed to stir for 15 minutes, after which the volatiles were removed under reduced pressure to provide the title compound in crude form. The crude compound was purified by column chromatography using a hexanes:ethyl acetate gradient (10-50%) to provide the title compound as a white solid (0.126 g, 91% yield) (M+H =463.2).

EXAMPLE 2 – Preparation of 2-Chloro-N-[1-(4-chlorobenzenesulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl]-6-fluorobenzamide (5)

[0227] The title compound was prepared according to the procedures described below.

Part I – Synthesis of 1-(4-Chlorobenzenesulfonyl)-7-nitro-1,2,3,4-tetrahydroquinoline

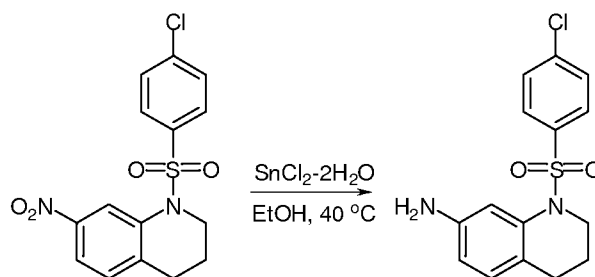


[0228] 7-Nitro-1,2,3,4-tetrahydroquinoline (500 mg, 2.8 mmol), 4-chlorobenzenesulfonyl chloride (700 mg, 3.3 mmol), and pyridine (1.5 mL) were combined in a microwave vial (5 mL) and heated in a microwave reactor at 120 °C for 10 minutes. The reaction mixture was

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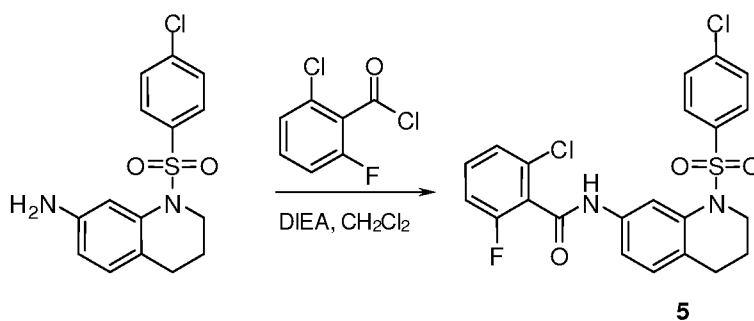
diluted with 1M HCl (aq) and extracted with CH₂Cl₂ (3 x 20 mL). The combined organic extracts were concentrated under reduced pressure and purified by column chromatography (EtOAc/hexanes) to afford 1-(4-chlorobenzene-sulfonyl)-7-nitro-1,2,3,4-tetrahydroquinoline as a solid (630 mg, 59%). LCMS (ESI): calcd. C₁₅H₁₃ClN₂O₄S, 352; found (M+H), 353.

5 Part II – Synthesis of 1-(4-Chlorobenzenesulfonyl)-1,2,3,4-tetrahydroquinolin-7-ylamine



[0229] 1-(4-Chlorobenzenesulfonyl)-7-nitro-1,2,3,4-tetrahydroquinoline (700 mg, 2.0 mmol) and SnCl₂·2H₂O (1.4 g, 6.2 mmol) were suspended in EtOH (10 mL) and stirred at 40 °C for 12 h. After cooling to room temperature, 2M KOH (aq) (10 mL) was added and the resulting mixture was extracted with CH₂Cl₂ (3 x 15 mL). The organic extracts were combined, dried (Na₂SO₄), and concentrated under reduced pressure to give 1-(4-chlorobenzenesulfonyl)-1,2,3,4-tetrahydroquinolin-7-ylamine as a crude solid (600 mg). LCMS (ESI): calcd. C₁₅H₁₅ClN₂O₂S, 322; found (M+H), 323.

15 Part III – Synthesis of 2-Chloro-*N*-[1-(4-chlorobenzenesulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl]-6-fluorobenzamide



[0230] A solution of 1-(4-chlorobenzenesulfonyl)-1,2,3,4-tetrahydroquinolin-7-ylamine (50 mg, 0.15 mmol), 2-chloro-6-fluorobenzoyl chloride (35 mg, 0.18 mmol), and *N,N*-diisopropylethylamine (DIEA, 0.055 mL, 0.32 mmol) in CH₂Cl₂ (1 mL) was stirred at room temperature for 3 h. The resulting solution was purified by HPLC to give 2-chloro-*N*-[1-(4-

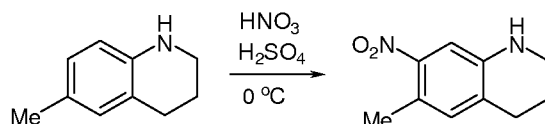
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chlorobenzenesulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl]-6-fluorobenzamide (36 mg, 50%).
LCMS (ESI): calcd. $C_{22}H_{17}Cl_2FN_2O_3S$, 478; found (M+H), 479.

EXAMPLE 3 – Preparation of 2-Chloro-6-fluoro-N-[1-(4-fluorobenzenesulfonyl)-6-methyl-1,2,3,4-tetrahydroquinolin-7-yl]benzamide (6)

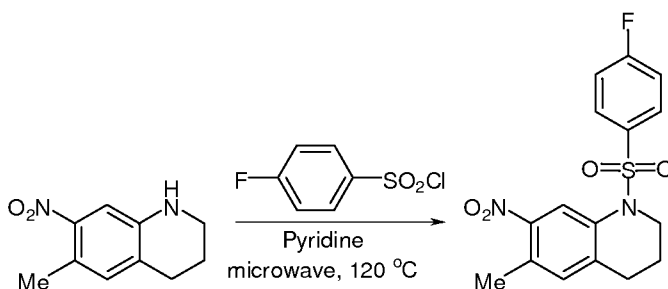
5 [0231] The title compound was prepared according to the procedures described below.

Part I – Synthesis of 6-Methyl-7-nitro-1,2,3,4-tetrahydroquinoline



[0232] 6-Methyl-1,2,3,4-tetrahydroquinoline (2.0 g, 14 mmol) was combined with H_2SO_4 (5 mL) and the resulting mixture was cooled to 0 °C. After a dropwise addition of a solution of
10 HNO_3 (850 mg, 14 mmol) and H_2SO_4 (1.5 mL) (combined at 0 °C and allowed to stir for 10 minutes), the reaction was allowed to stir for 2 h. The reaction mixture was poured over ice and neutralized with aqueous $NaHCO_3$. The product was extracted with CH_2Cl_2 (3 x 30 mL). The organic extracts were combined, dried over Na_2SO_4 , and concentrated under reduced pressure to give 6-methyl-7-nitro-1,2,3,4-tetrahydroquinoline as the major isomer in a 2:1
15 isomeric mixture (1.8 g). The mixture was used in the next step without purification.

Part II – Synthesis of 1-(4-Fluorobenzenesulfonyl)-6-methyl-7-nitro-1,2,3,4-tetrahydroquinoline



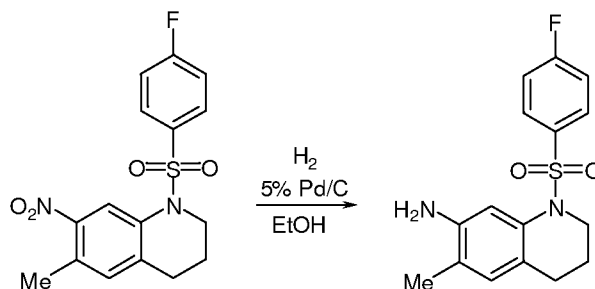
[0233] 6-Methyl-7-nitro-1,2,3,4-tetrahydroquinoline (2.6 g, 14 mmol), 4-fluorobenzenesulfonyl chloride (3.2 g, 16 mmol), and pyridine (4 mL) were combined in a microwave vial (10 mL) and heated in a microwave reactor at 120 °C for 10 minutes. The reaction mixture was poured over a 1M HCl solution and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were concentrated under reduced pressure and purified by

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column chromatography (EtOAc/hexanes) to afford 1-(4-fluorobenzenesulfonyl)-6-methyl-7-nitro-1,2,3,4-tetrahydroquinoline as a solid.

Part III – Synthesis of 1-(4-Fluorobenzenesulfonyl)-6-methyl-1,2,3,4-tetrahydroquinolin-7-ylamine

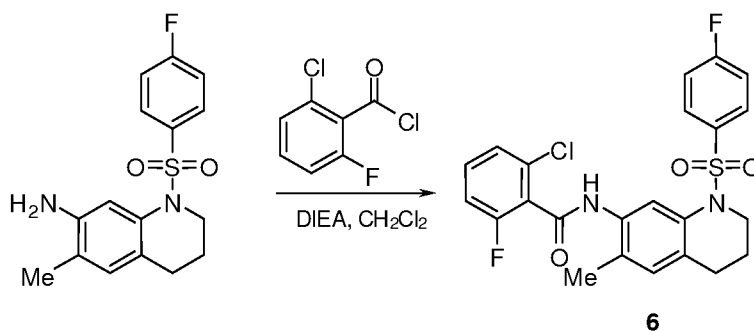
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[0234] 1-(4-Fluorobenzenesulfonyl)-6-methyl-7-nitro-1,2,3,4-tetrahydroquinoline (2.0 g, 5.7 mmol), 5% Pd/C (200 mg), and EtOH (30 mL) were agitated under a hydrogen atmosphere (30 p.s.i.) for 1 h using a Parr shaker. The resulting mixture was filtered through celite and concentrated under reduced pressure to give 1-(4-fluorobenzenesulfonyl)-6-methyl-1,2,3,4-tetrahydroquinolin-7-ylamine (1.7 g, 91%) as a solid. LCMS (ESI): calcd. $C_{16}H_{17}FN_2O_2S$, 320; found (M+H), 321.

10

Part IV – Synthesis of 2-Chloro-6-fluoro-N-[1-(4-fluorobenzenesulfonyl)-6-methyl-1,2,3,4-tetrahydroquinolin-7-yl]benzamide



6

[0235] A solution of 1-(4-fluorobenzenesulfonyl)-6-methyl-1,2,3,4-tetrahydroquinolin-7-ylamine (50 mg, 0.16 mmol), 2-chloro-6-fluorobenzoyl chloride (35 mg, 0.18 mmol), and DIEA (0.055 mL, 0.32 mmol) in CH_2Cl_2 (1 mL) was stirred at room temperature for 3 h. The resulting solution was purified by HPLC to give 2-chloro-6-fluoro-N-[1-(4-fluorobenzenesulfonyl)-6-methyl-1,2,3,4-tetrahydroquinolin-7-yl]-benzamide (27 mg, 36%).

LCMS (ESI): calcd. $C_{23}H_{19}ClF_2N_2O_3S$, 476; found (M+H), 477.

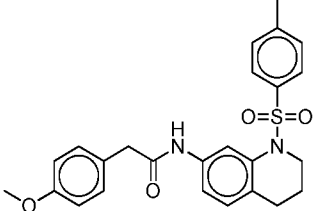
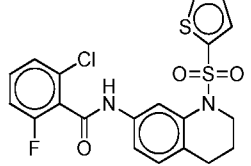
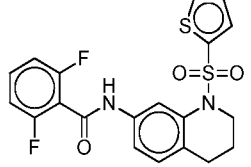
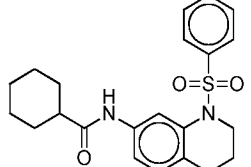
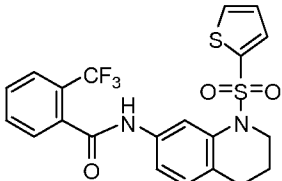
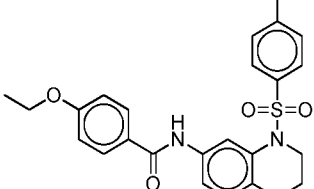
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EXAMPLE 4 – Preparation of Additional Tetrahydroquinoline Compounds

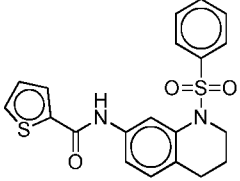
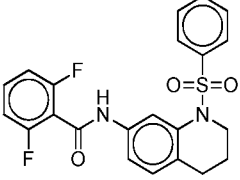
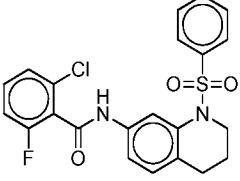
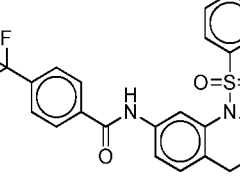
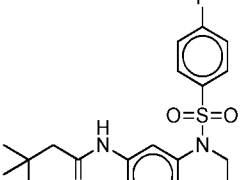
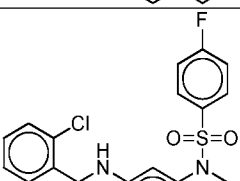
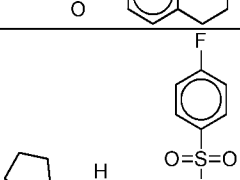
[0236] The compounds in Table 3 below were prepared based on the experimental procedures described in Examples 1-3 and in the detailed description. Starting materials can be obtained from commercial sources or readily prepared from commercially available materials.

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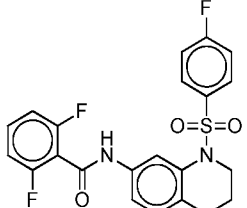
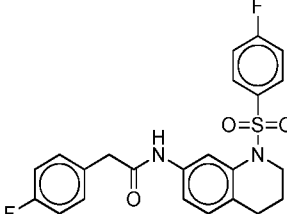
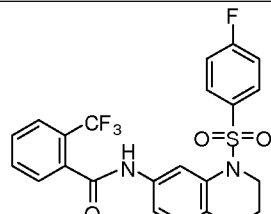
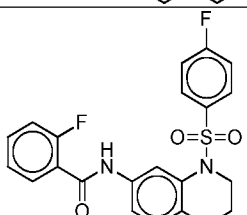
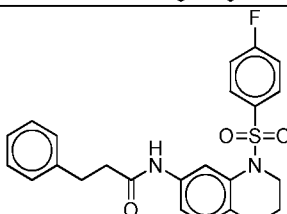
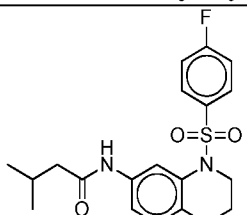
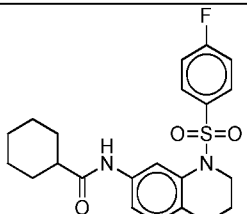
TABLE 3.

Compound No.	Chemical Structure
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III-2	
III-3	
III-4	
III-5	
III-6	

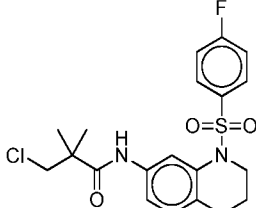
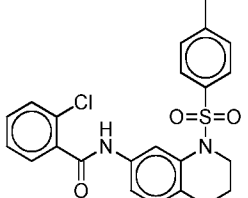
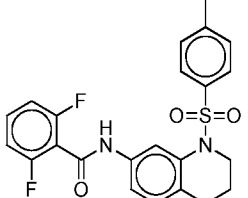
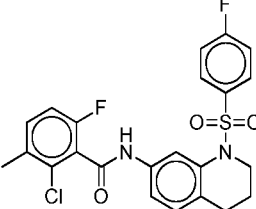
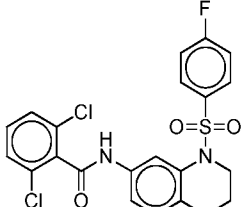
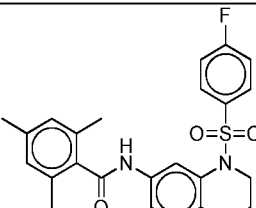
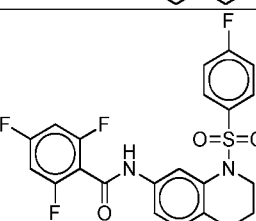
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Compound No.	Chemical Structure
III-7	
III-8	
III-9	
III-10	
III-11	
III-12	
III-13	

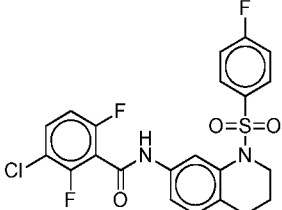
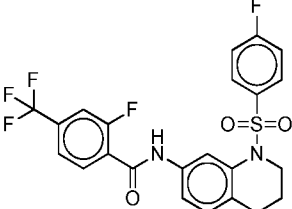
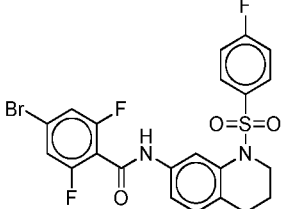
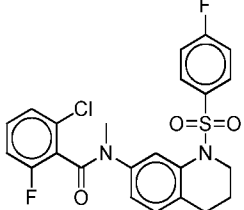
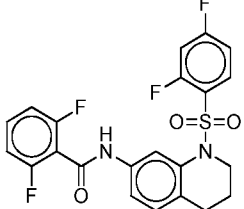
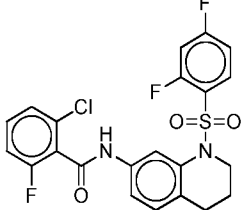
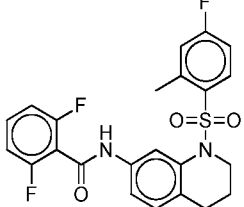
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Compound No.	Chemical Structure
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III-15	
III-16	
III-17	
III-18	
III-19	
III-20	

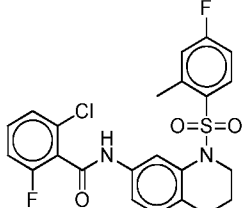
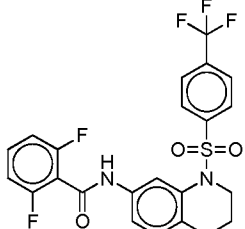
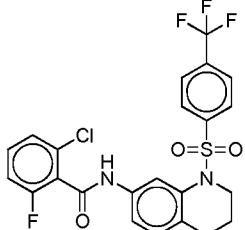
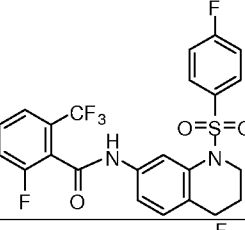
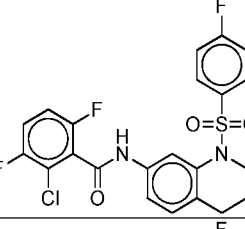
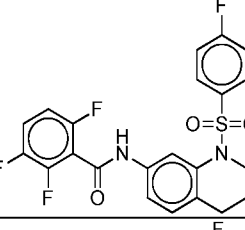
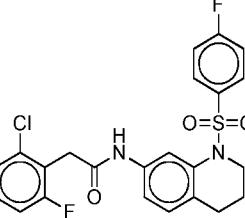
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Compound No.	Chemical Structure
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III-22	
III-23	
III-24	
III-25	
III-26	
III-27	

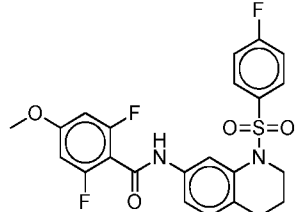
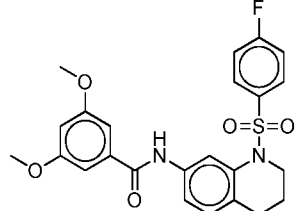
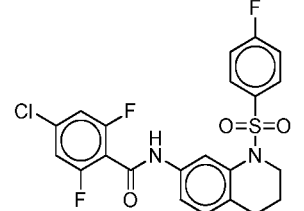
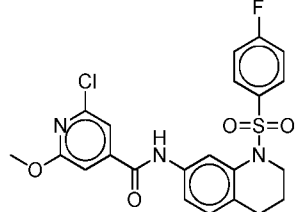
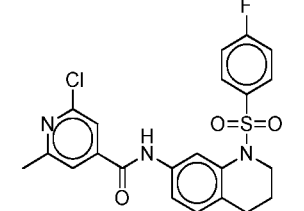
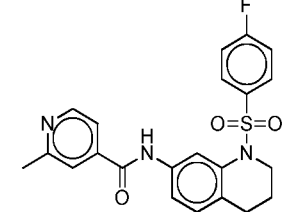
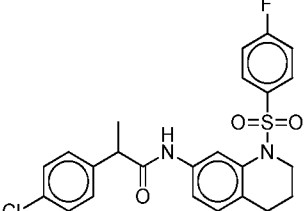
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Compound No.	Chemical Structure
III-28	
III-29	
III-30	
III-31	
III-32	
III-33	
III-34	

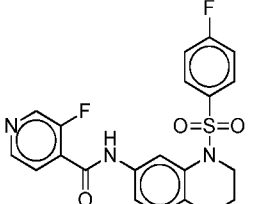
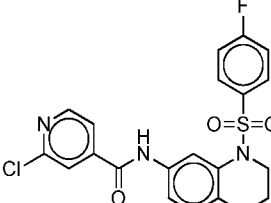
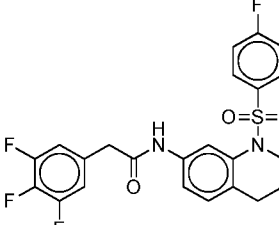
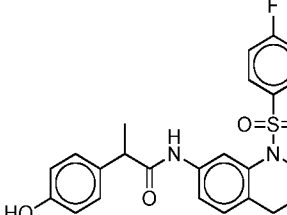
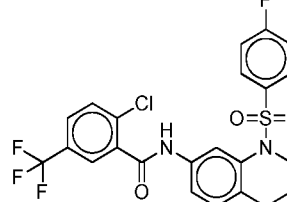
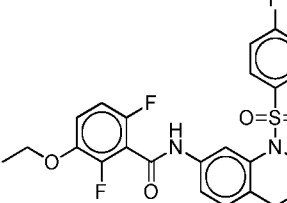
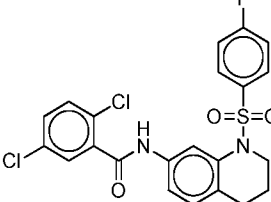
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Compound No.	Chemical Structure
III-35	
III-36	
III-37	
III-38	
III-39	
III-40	
III-41	

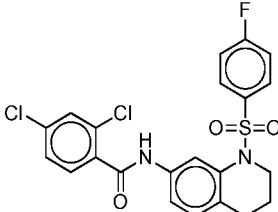
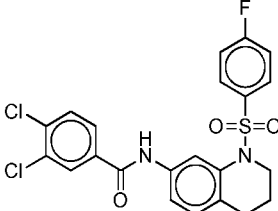
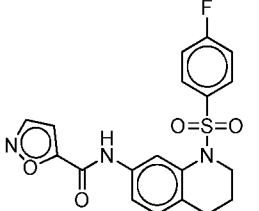
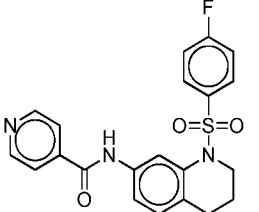
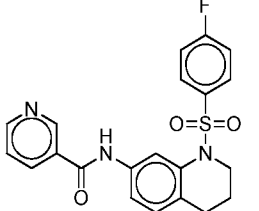
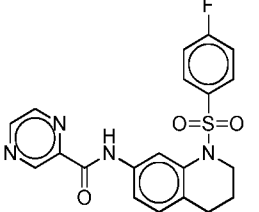
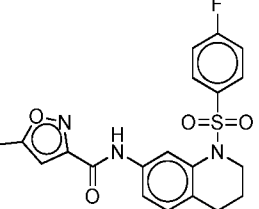
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Compound No.	Chemical Structure
III-42	
III-43	
III-44	
III-45	
III-46	
III-47	
III-48	

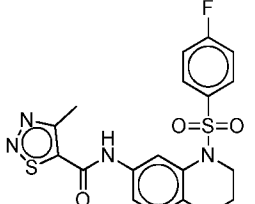
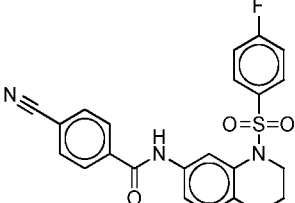
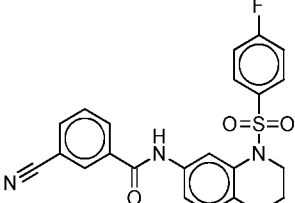
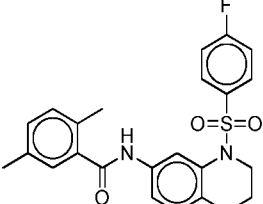
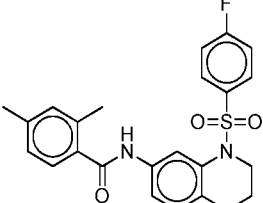
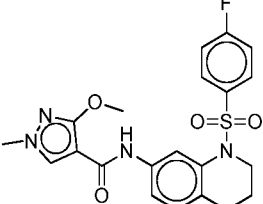
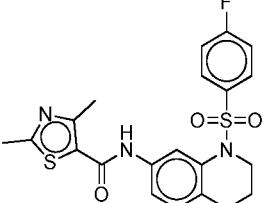
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Compound No.	Chemical Structure
III-49	
III-50	
III-51	
III-52	
III-53	
III-54	
III-55	

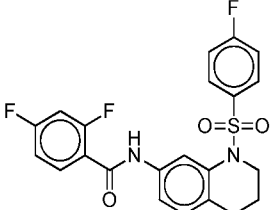
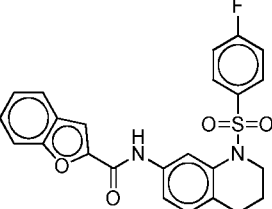
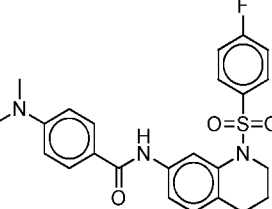
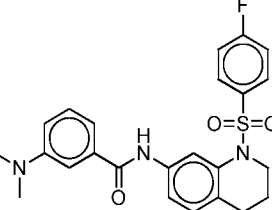
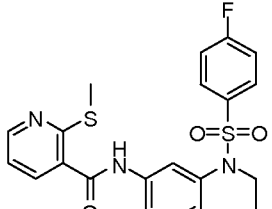
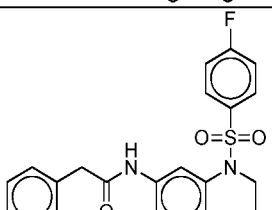
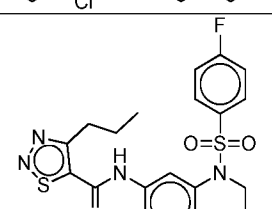
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Compound No.	Chemical Structure
III-56	
III-57	
III-58	
III-59	
III-60	
III-61	
III-62	

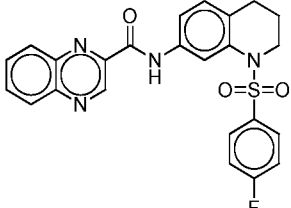
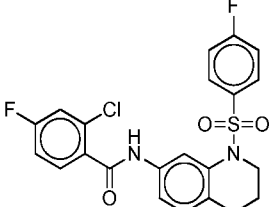
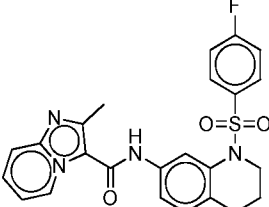
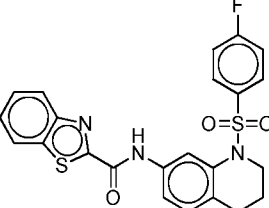
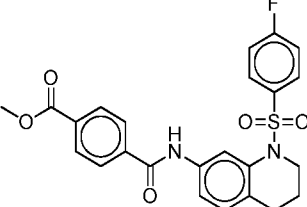
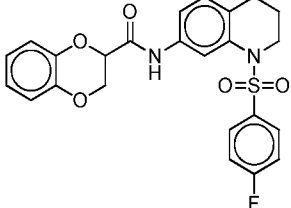
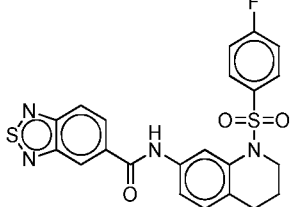
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Compound No.	Chemical Structure
III-63	
III-64	
III-65	
III-66	
III-67	
III-68	
III-69	

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Compound No.	Chemical Structure
III-70	
III-71	
III-72	
III-73	
III-74	
III-75	
III-76	

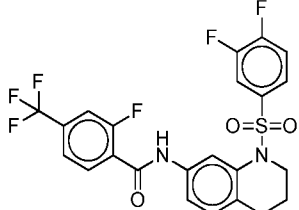
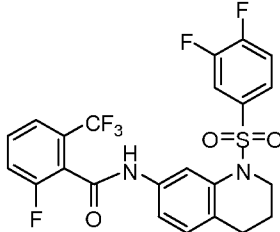
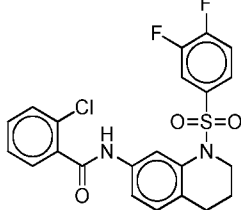
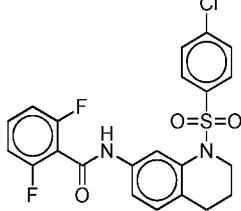
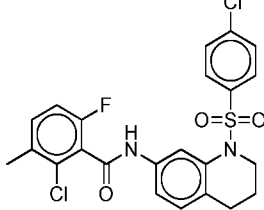
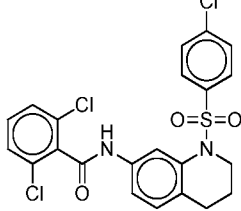
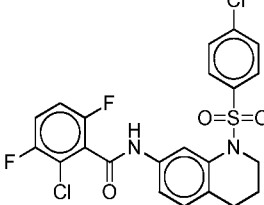
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Compound No.	Chemical Structure
III-77	
III-78	
III-79	
III-80	
III-81	
III-82	
III-83	

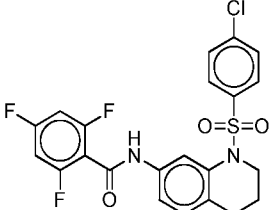
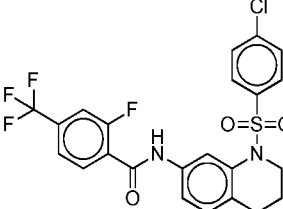
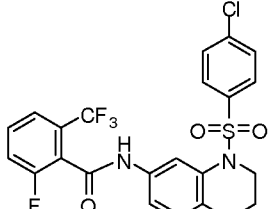
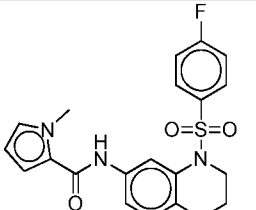
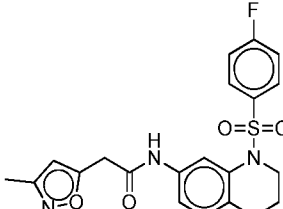
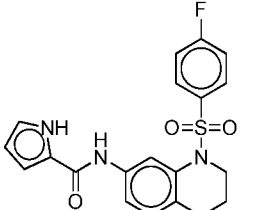
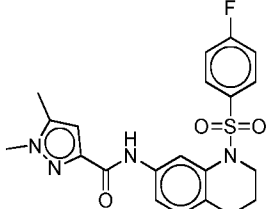
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Compound No.	Chemical Structure
III-84	
III-85	
III-86	
III-87	
III-88	
III-89	
III-90	

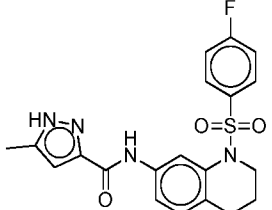
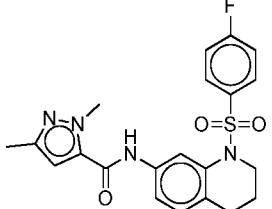
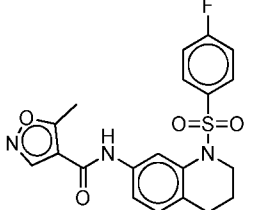
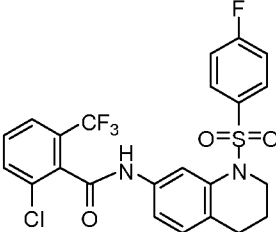
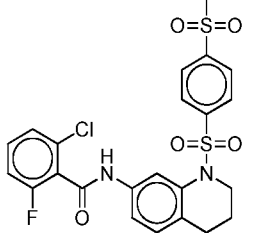
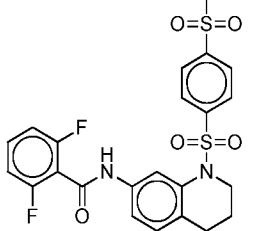
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Compound No.	Chemical Structure
III-91	
III-92	
III-93	
III-94	
III-95	
III-96	
III-97	

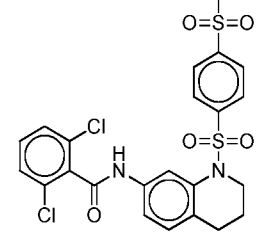
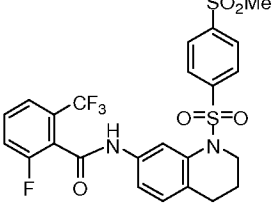
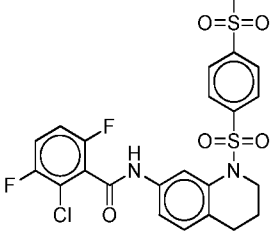
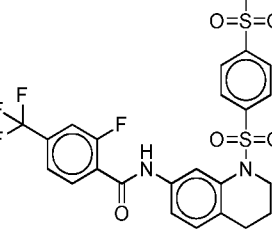
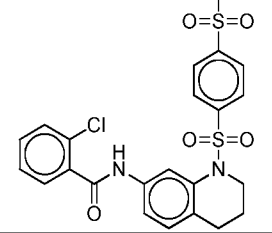
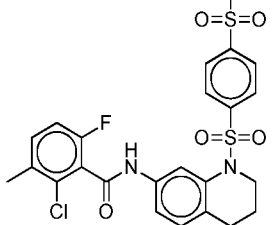
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Compound No.	Chemical Structure
III-98	
III-99	
III-100	
III-101	
III-102	
III-103	
III-104	

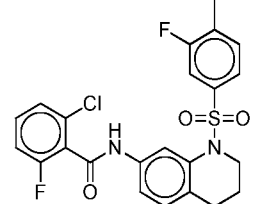
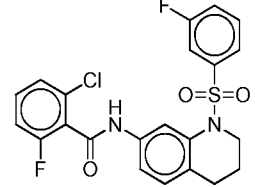
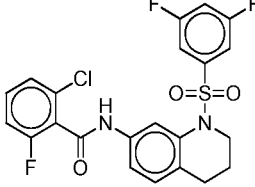
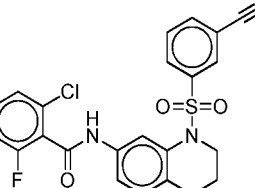
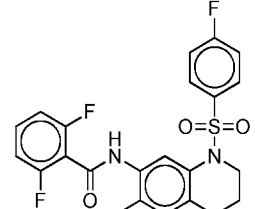
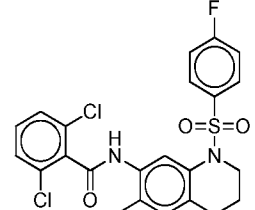
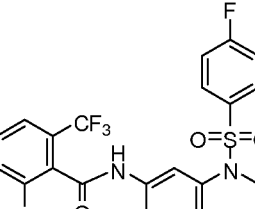
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Compound No.	Chemical Structure
III-105	
III-106	
III-107	
III-108	
III-109	
III-110	

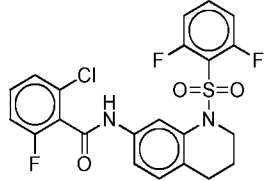
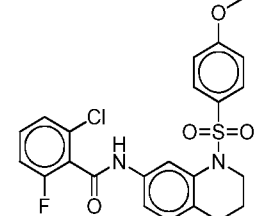
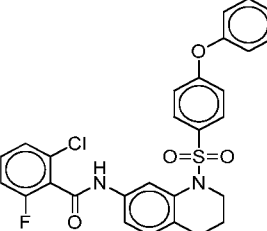
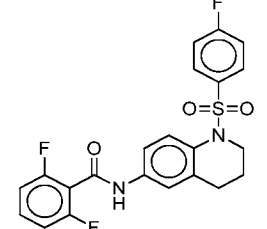
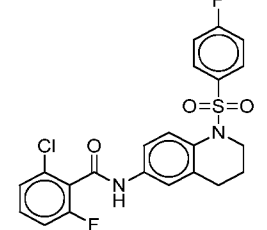
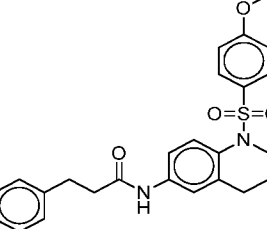
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Compound No.	Chemical Structure
III-111	
III-112	
III-113	
III-114	
III-115	
III-116	

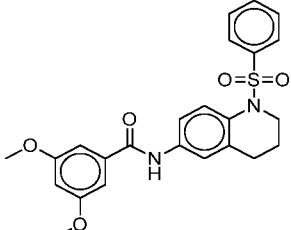
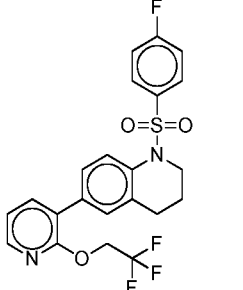
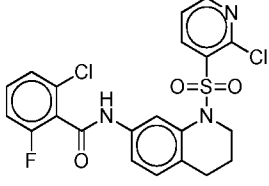
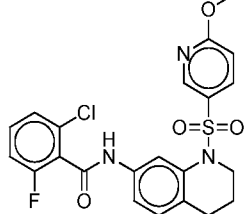
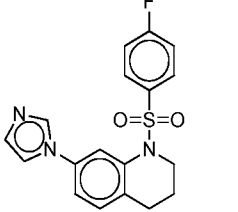
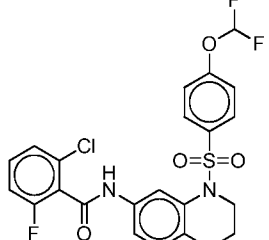
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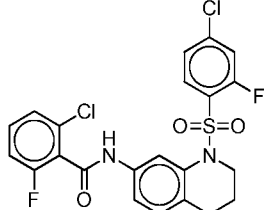
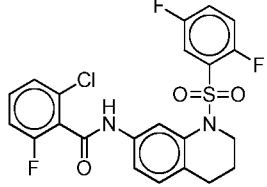
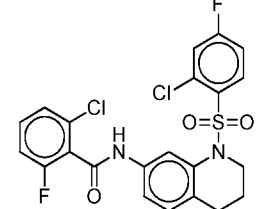
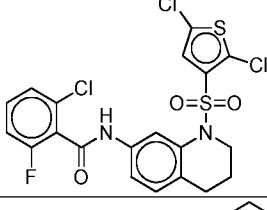
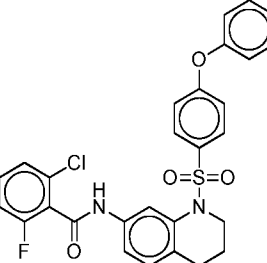
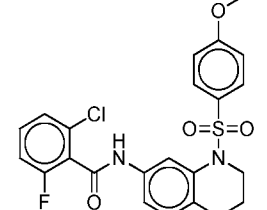
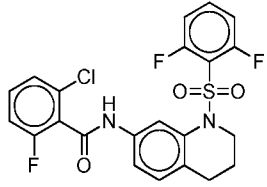
Compound No.	Chemical Structure
III-117	
III-118	
III-119	
III-120	
III-121	
III-122	
III-123	

- 126 -

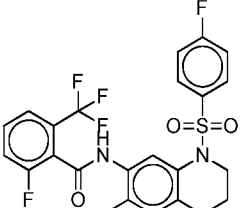
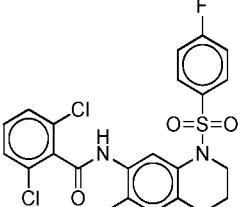
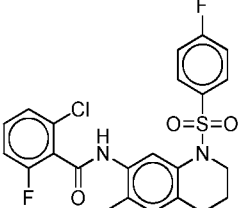
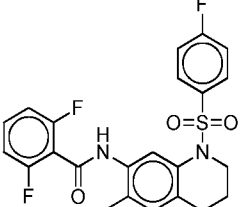
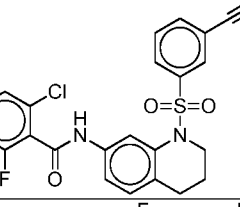
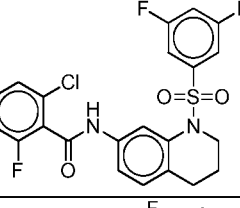
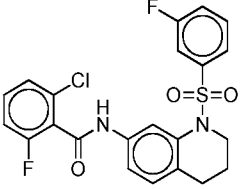
Compound No.	Chemical Structure
III-124	
III-125	
III-126	
III-127	
III-128	
III-129	

- 127 -

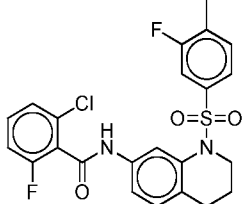
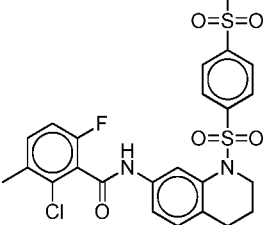
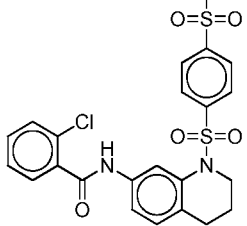
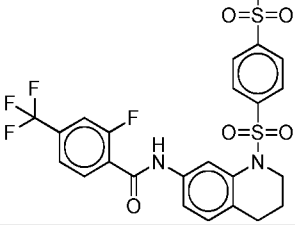
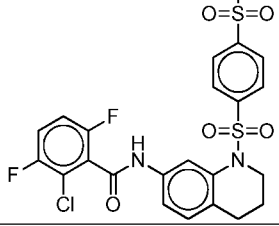
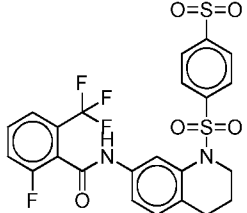
Compound No.	Chemical Structure
III-130	
III-131	
III-132	
III-133	
III-134	
III-135	

Compound No.	Chemical Structure
III-136	
III-137	
III-138	
III-139	
III-140	
III-141	
III-142	

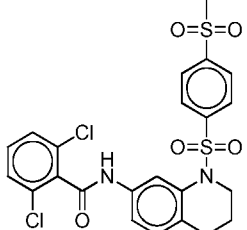
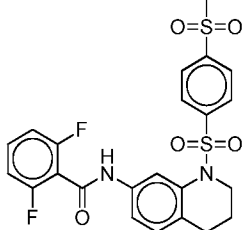
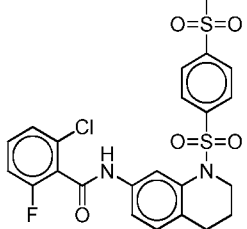
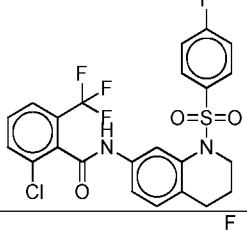
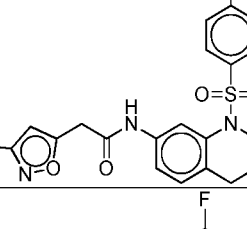
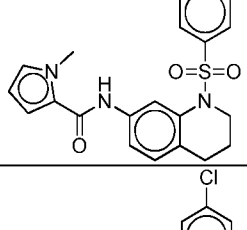
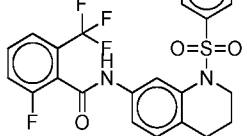
- 129 -

Compound No.	Chemical Structure
III-143	
III-144	
III-145	
III-146	
III-147	
III-148	
III-149	

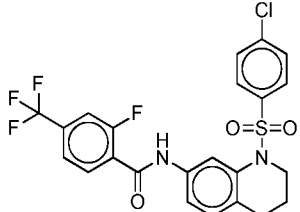
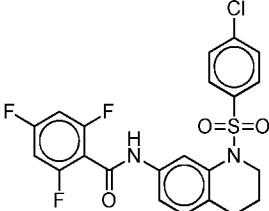
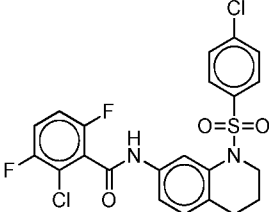
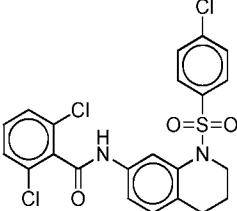
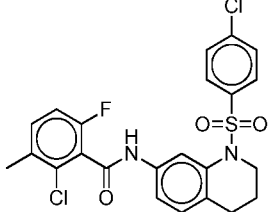
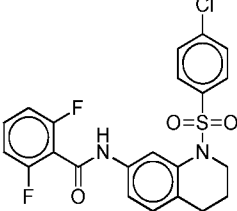
- 130 -

Compound No.	Chemical Structure
III-150	
III-151	
III-152	
III-153	
III-154	
III-155	

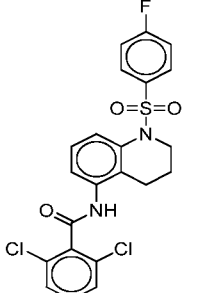
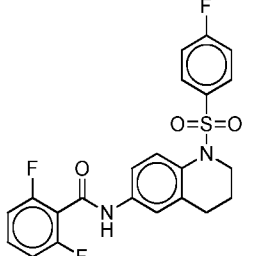
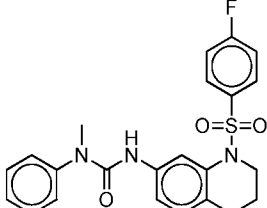
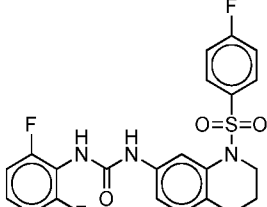
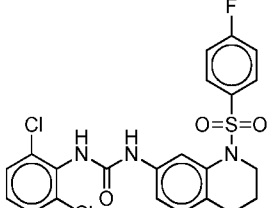
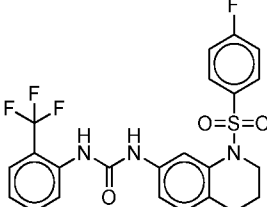
- 131 -

Compound No.	Chemical Structure
III-156	
III-157	
III-158	
III-159	
III-160	
III-161	
III-162	

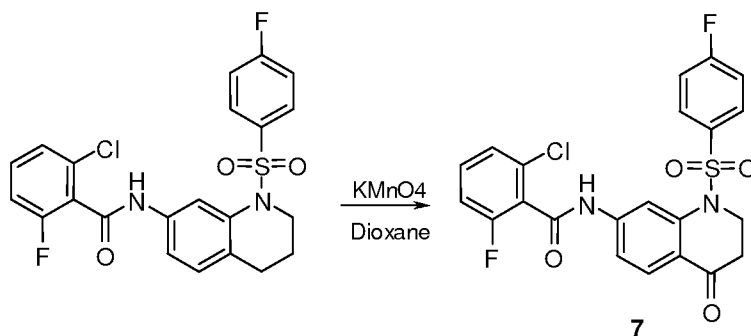
- 132 -

Compound No.	Chemical Structure
III-163	
III-164	
III-165	
III-166	
III-167	
III-168	

- 133 -

Compound No.	Chemical Structure
III-169	
III-170	
III-171	
III-172	
III-173	
III-174	

EXAMPLE 5 – Preparation of 2-Chloro-6-fluoro-N-[1-(4-fluorobenzenesulfonyl)-4-oxo-1,2,3,4-tetrahydroquinolin-7-yl]benzamide (7) & Related Compounds



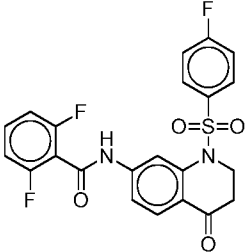
[0237] A solution of 2-chloro-N-[1-(4-fluorobenzenesulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl]-6-fluorobenzamide (100 mg, 0.2 mmol, Example 3) and KMnO_4 (130 mg, 0.82 mmol) in dioxane (1 mL) was stirred for 24 h at room temperature. The reaction mixture was concentrated under reduced pressure and then suspended in a H_2O /acetone solution (50:1, 5 mL). The remaining purple color disappeared after 10 minutes and the aqueous layer was extracted with EtOAc (3 x 5 mL). The product was purified by column chromatography (EtOAc/hexanes) and followed by HPLC purification to give 2-chloro-6-fluoro-N-[1-(4-fluorobenzenesulfonyl)-4-oxo-1,2,3,4-tetrahydroquinolin-7-yl]-benzamide (23 mg, 24%). ^1H NMR 250MHz CDCl_3 δ 8.1 – 7.7 (m, 5H), 7.5 – 7.0 (m, 5H), 4.23 (t, J = 6.5 Hz, 2H), 4.67 (t, J = 6.5 Hz, 2H). LCMS (ESI): calcd. $\text{C}_{22}\text{H}_{15}\text{ClF}_2\text{N}_2\text{O}_4\text{S}$, 476; found (M+H), 477.

[0238] The compounds in Table 4 below were prepared based on the above procedure. Starting materials can be obtained from commercial sources or readily prepared from commercially available materials.

TABLE 4.

Compound No.	Chemical Structure
IV-1	

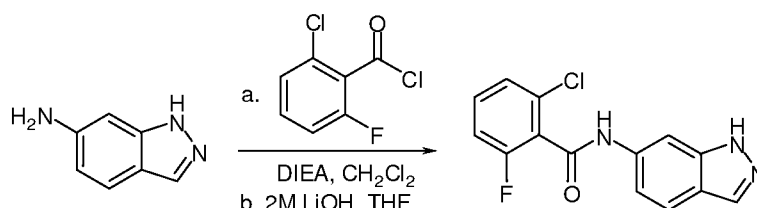
- 135 -

Compound No.	Chemical Structure
IV-2	

EXAMPLE 6 – Preparation of 2-Chloro-6-fluoro-N-[1-(4-fluorobenzenesulfonyl)-1H-indazol-6-yl]benzamide (8)

[0239] The title compound was prepared according to the procedures described below.

Part I – Synthesis of 2-Chloro-6-fluoro-N-(1H-indazol-6-yl)benzamide



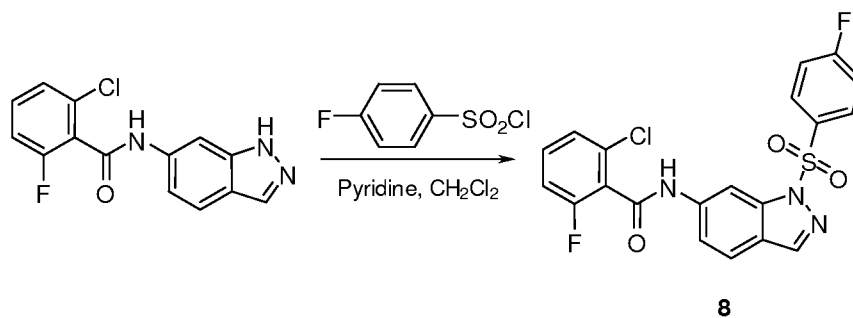
[0240] To a suspension of 6-aminoindazole (1 g, 7.5 mmol) and DIEA (4 mL) in CH₂Cl₂ (20 mL) was added 2-chloro-6-fluorobenzoyl chloride (2.9 g, 15 mmol) dropwise at -10 °C. The reaction mixture was stirred for 12 h at room temperature and was diluted with EtOAc, washed with 1M HCl, aqueous NaHCO₃, and brine. The organic extract was dried over Na₂SO₄ and concentrated under reduced pressure to give a crude mixture of the mono-acylation and bis-acylation products. To the product mixture in THF (20 mL) was added 2M LiOH (aq) (10 mL) and the reaction was stirred for 12 h at 60 °C. The organic solvent was removed under reduced pressure and the remaining aqueous mixture was acidified to pH ~ 4 with 1M HCl (aq). The resulting solution was extracted with EtOAc (3 x 20 mL), and the organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure to give 2-chloro-6-fluoro-N-(1H-indazol-6-yl)benzamide (1.3 g, 60%). LCMS (ESI): calcd. C₁₄H₉ClFN₃O, 289; found (M+H), 290.

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Part II – Synthesis of 2-Chloro-6-fluoro-*N*-[1-(4-fluorobenzenesulfonyl)-1H-indazol-6-yl]benzamide

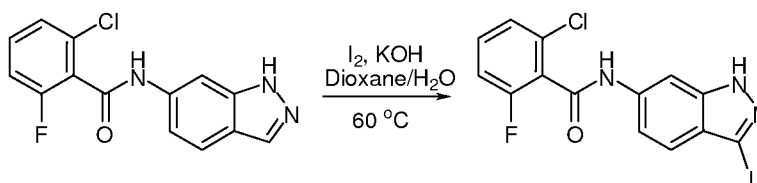


[0241] A solution of 2-chloro-6-fluoro-*N*-(1H-indazol-6-yl)benzamide (29 mg, 0.10 mmol) and 4-fluorobenzene-sulfonyl chloride (39 mg, 0.20 mmol) in CH₂Cl₂ (0.200 mL) and pyridine (0.200 mL) was stirred for 12 h at 60 °C. The reaction mixture was concentrated under reduced pressure, dissolved in DMSO and purified by HPLC to afford 2-chloro-6-fluoro-*N*-[1-(4-fluorobenzenesulfonyl)-1H-indazol-6-yl]benzamide. LCMS (ESI): calcd. C₂₀H₁₂ClF₂N₃O₃S, 447; found (M+H), 448.

10 **EXAMPLE 7 – Preparation of 2-Chloro-6-fluoro-*N*-[1-(3-trifluoromethylbenzenesulfonyl)-3-vinyl-1H-indazol-6-yl]benzamide (9)**

[0242] The title compound was prepared according to the procedures described below.

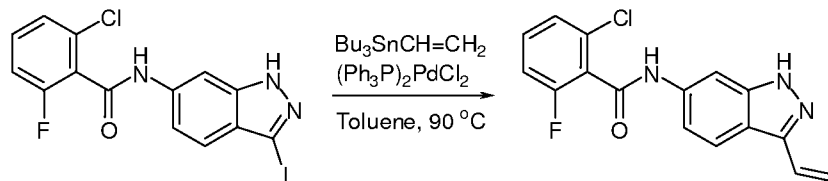
Part I – Synthesis of 2-Chloro-6-fluoro-*N*-(3-iodo-1H-indazol-6-yl)benzamide



15 **[0243]** To a suspension of 2-chloro-6-fluoro-*N*-(1H-indazol-6-yl)benzamide (600 mg, 2.1 mmol) and KOH (210 mg, 3.8 mmol) in dioxane (6 mL) and H₂O (0.600 mL) was added I₂ (630 mg, 2.5 mmol) and the reaction was stirred at 60 °C for 1 h. The reaction was cooled to room temperature and diluted with H₂O (20 mL). The resulting light brown solid was filtered and dried under reduced pressure to give 2-chloro-6-fluoro-*N*-(3-iodo-1H-indazol-6-yl)benzamide (850 mg, 97%). LCMS (ESI): calcd. C₁₄H₈ClFIN₃O, 415; found (M+H), 416.

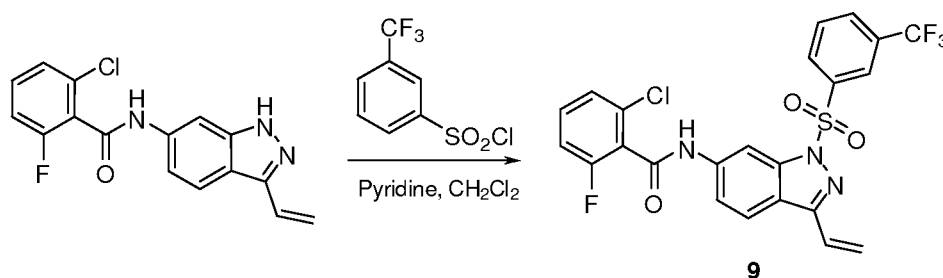
20

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Part II – Synthesis of 2-Chloro-6-fluoro-N-(3-vinyl-1H-indazol-6-yl)benzamide

[0244] A suspension of 2-chloro-6-fluoro-N-(3-iodo-1H-indazol-6-yl)benzamide (200 mg, 0.48 mmol), tributyl(vinyl)tin (210 mg, 0.67 mmol), and bis(triphenylphosphine)palladium(II) dichloride (34 mg, 0.048 mmol) in toluene (6 mL) was heated at 90 °C for 4 h. The reaction was concentrated under reduced pressure and purified by column chromatography (EtOAc/hexanes) to give 2-chloro-6-fluoro-N-(3-vinyl-1H-indazol-6-yl)benzamide (90 mg, contaminated with organic tin byproducts). This mixture was used in the next step without further purification. LCMS (ESI): calcd. C₁₆H₁₁ClFN₃O, 315; found (M+H), 316.

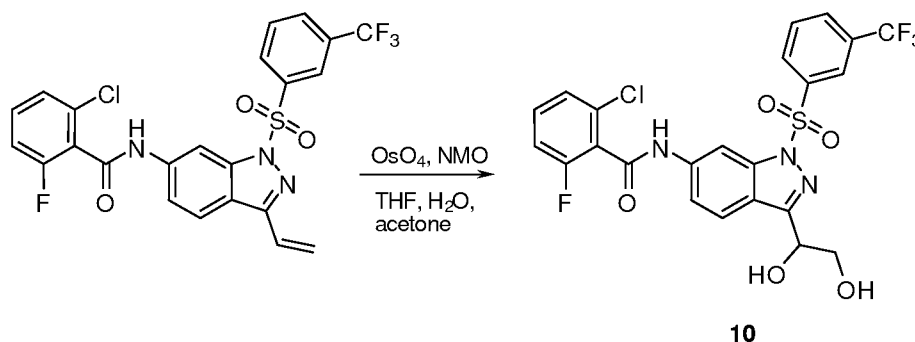
10 **Part III – Synthesis of 2-Chloro-6-fluoro-N-[1-(3-trifluoromethylbenzenesulfonyl)-3-vinyl-1H-indazol-6-yl]benzamide**



[0245] A solution of 2-chloro-6-fluoro-N-(3-vinyl-1H-indazol-6-yl)benzamide (90 mg, 0.29 mmol) and 3-(trifluoromethyl)benzenesulfonyl chloride (110 mg, 0.43 mmol) in pyridine (2 mL) and CH₂Cl₂ (2 mL) was stirred for 12 h at 65 °C. The reaction mixture was cooled to room temperature and washed with 1M HCl (aq), saturated NaHCO₃ (aq), and brine. The organic extracts were dried (Na₂SO₄), concentrated under reduced pressure, and purified by column chromatography (EtOAc/hexanes) to give 2-chloro-6-fluoro-N-[1-(3-trifluoromethylbenzenesulfonyl)-3-vinyl-1H-indazol-6-yl]benzamide (125 mg, contaminated with organic tin byproducts). A small portion (~ 5 mg) was successfully purified by HPLC while the rest was used in the next reaction without further purification. LCMS (ESI): calcd. C₂₃H₁₄ClF₄N₃O₃S, 523; found (M+H), 524.

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EXAMPLE 8 – Preparation of 2-Chloro-*N*-[3-(1,2-dihydroxyethyl)-1-(3-trifluoromethylbenzenesulfonyl)-1H-indazol-6-yl]-6-fluorobenzamide (10)



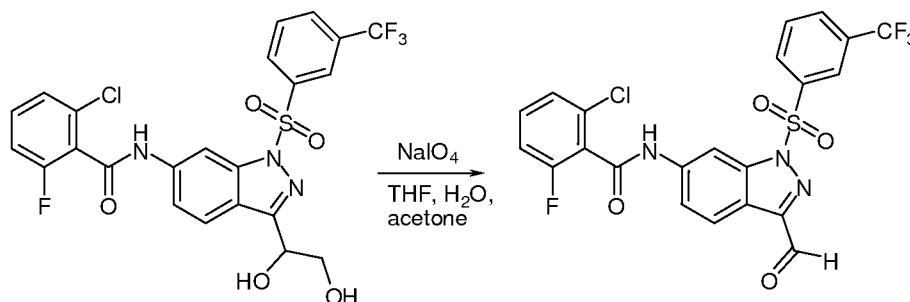
[0246] To a solution of 2-chloro-6-fluoro-*N*-[1-(3-(trifluoromethyl)benzenesulfonyl)-3-vinyl-1H-indazol-6-yl]benzamide (120 mg, 0.23 mmol) in THF/acetone/H₂O (1:1:1, 1.2 mL) was added *N*-methylmorpholine-*N*-oxide (NMO, 40 mg, 0.31 mmol) and OsO₄ (2.5 wt% solution in *t*-BuOH, 0.320 mL). The reaction was stirred for 3 h at room temperature. Sodium bisulfite (260 mg, 2.3 mmol) in H₂O (6 mL) was added and the solution was stirred for 10 minutes. The solution was diluted with brine and the product was extracted with EtOAc (3 x 10 mL). The organic extracts were dried (Na₂SO₄), concentrated under reduced pressure, and purified by column chromatography (EtOAc, hexanes) to give 2-chloro-*N*-[3-(1,2-dihydroxyethyl)-1-(3-(trifluoromethyl)benzenesulfonyl)-1H-indazol-6-yl]-6-fluorobenzamide (70 mg, 55%). ¹H NMR 250MHz CDCl₃ (with 5% CD₃OD) δ 8.49 (d, J = 1.6 Hz, 1H), 8.23 (s, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.62 (dd, J = 8.8, 1.8 Hz, 1H), 7.60 (t, 8.3 Hz, 1H), 7.34 (td, 8.0, 5.8 Hz, 1H), 7.24 (d, 8.0 Hz, 1H), 7.08 (t, J = 8.3 Hz, 1H), 5.03 (t, J = 5.5 Hz, 1H), 3.84 (d, J = 5.5 Hz, 2H). LCMS (ESI): calcd. C₂₃H₁₆ClF₄N₃O₅S, 557; found (M+H), 558.

EXAMPLE 9 – Preparation of 2-Chloro-6-fluoro-*N*-[3-hydroxymethyl-1-(3-trifluoromethylbenzene-sulfonyl)-1H-indazol-6-yl]benzamide (11)

[0247] The title compound was prepared according to the procedures described below.

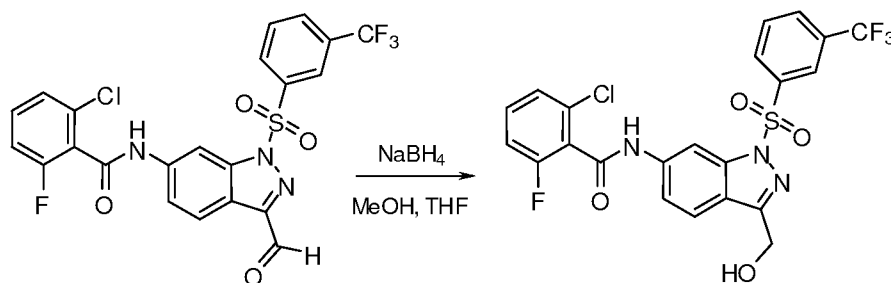
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Part I – Synthesis of 2-Chloro-6-fluoro-*N*-[3-formyl-1-(3-trifluoromethylbenzenesulfonyl)-1H-indazol-6-yl]benzamide



- [0248] To a solution of 2-chloro-*N*-[3-(1,2-dihydroxyethyl)-1-(3-trifluoromethylbenzenesulfonyl)-1H-indazol-6-yl]-6-fluorobenzamide (60 mg, 0.11 mmol) in THF (0.200 mL) and THF/acetone/H₂O (1:1:1, 2 mL) was added NaIO₄ (40 mg, 0.2 mmol). The reaction was stirred at room temperature for 12 h. Brine was added and the product was extracted with EtOAc (3 x 10 mL). The organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure to give 2-chloro-6-fluoro-*N*-[3-formyl-1-(3-trifluoromethylbenzenesulfonyl)-1H-indazol-6-yl]benzamide (35 mg, crude). LCMS (ESI): calcd. C₂₂H₁₂ClF₄N₃O₄S, 525; found (M+H), 526.

Part II – Synthesis of 2-Chloro-6-fluoro-*N*-[3-hydroxymethyl-1-(3-trifluoromethylbenzene-sulfonyl)-1H-indazol-6-yl]benzamide



11

- [0249] 2-Chloro-6-fluoro-*N*-[3-formyl-1-(3-trifluoromethylbenzenesulfonyl)-1H-indazol-6-yl]benzamide (30 mg, 0.06 mmol) and NaBH₄ (10 mg, 0.26 mmol) were dissolved in MeOH/THF (1:2, 1 mL) and stirred for 1 h at room temperature. The organic solvents were removed and the product was purified by column chromatography (EtOAc/hexanes) to give 2-chloro-6-fluoro-*N*-[3-hydroxymethyl-1-(3-trifluoro-methylbenzenesulfonyl)-1H-indazol-6-yl]benzamide (20 mg, 60%). ¹H NMR 250MHz CDCl₃ (with 5% CD₃OD) δ 8.50 (d, J = 1.6 Hz,

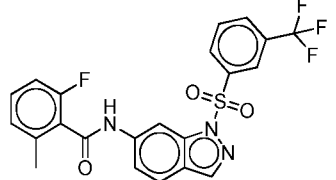
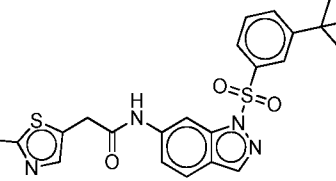
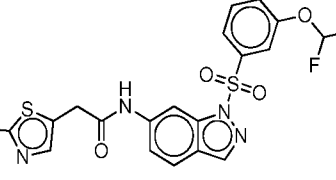
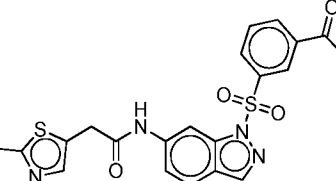
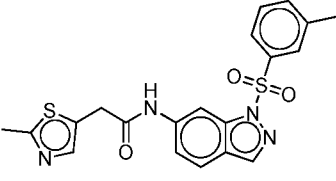
- 140 -

1H), 8.22 (s, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.5 Hz, 2H), 7.63 (dd, J = 8.8, 1.8 Hz, 1H), 7.59 (t, 8.0 Hz, 1H), 7.33 (td, 8.2, 6.0 Hz, 1H), 7.22 (d, 8.0 Hz, 1H), 7.06 (t, J = 8.5 Hz, 1H), 4.83 (s, 2H). LCMS (ESI): calcd. C₂₂H₁₄ClF₄N₃O₄S, 527; found (M+H), 528.

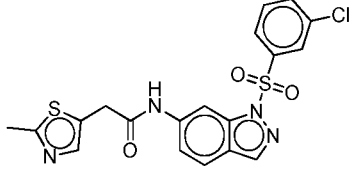
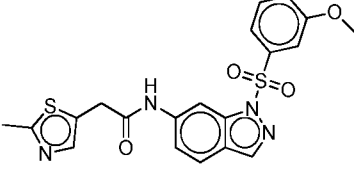
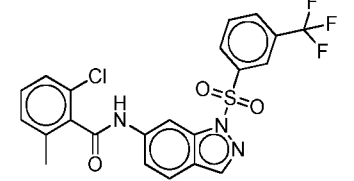
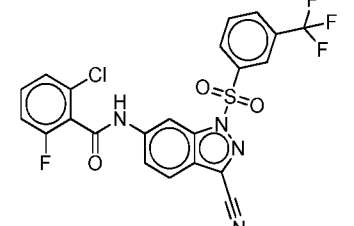
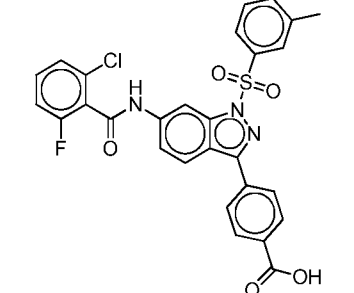
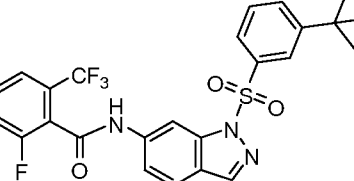
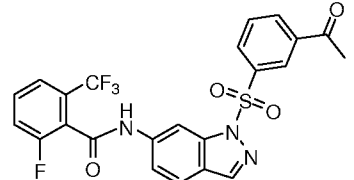
EXAMPLE 10 – Preparation of Additional Indazole Compounds

- 5 [0250] The compounds in Table 5 below were prepared based on the experimental procedures described in Examples 6-9 and in the detailed description. Starting materials can be obtained from commercial sources or readily prepared from commercially available materials.

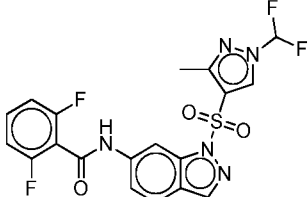
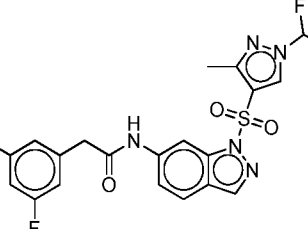
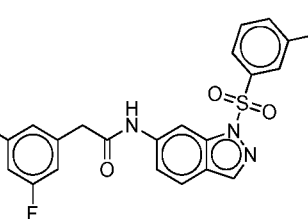
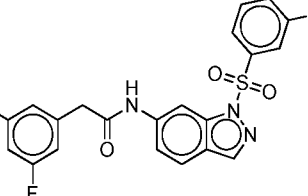
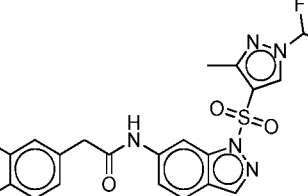
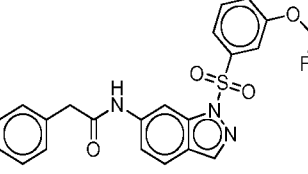
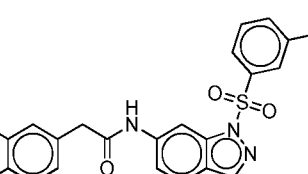
TABLE 5.

Compound No.	Chemical Structure
V-1	
V-2	
V-3	
V-4	
V-5	

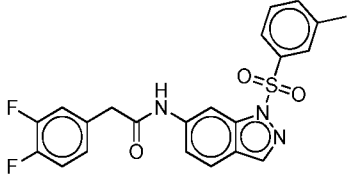
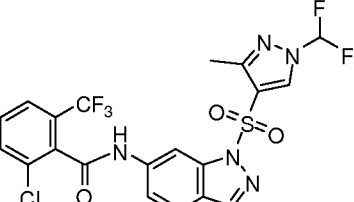
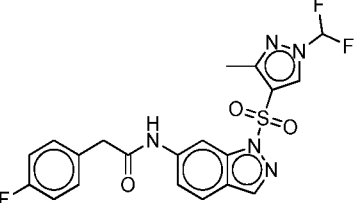
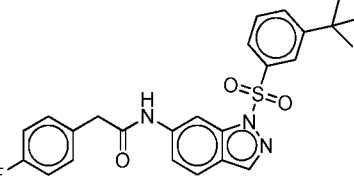
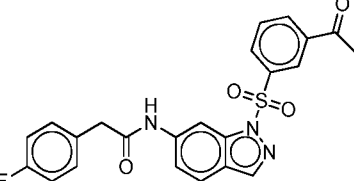
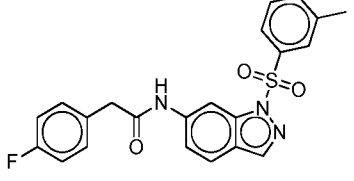
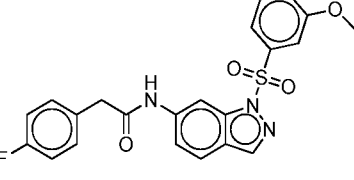
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Compound No.	Chemical Structure
V-6	
V-7	
V-8	
V-9	
V-10	
V-11	
V-12	

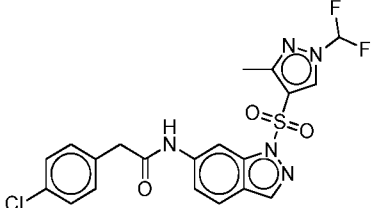
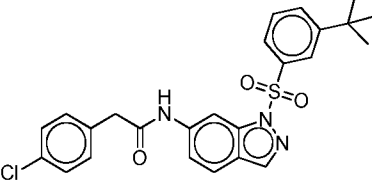
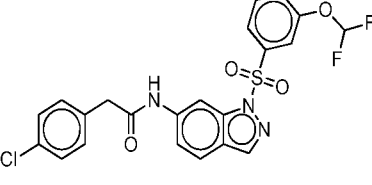
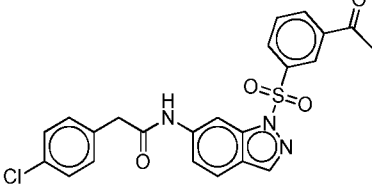
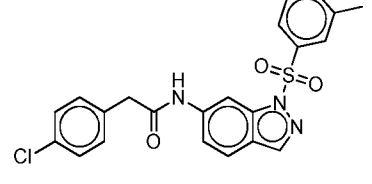
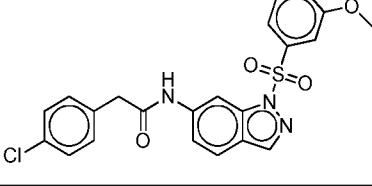
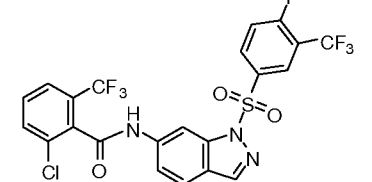
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Compound No.	Chemical Structure
V-13	
V-14	
V-15	
V-16	
V-17	
V-18	
V-19	

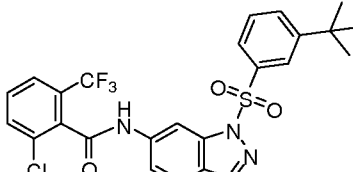
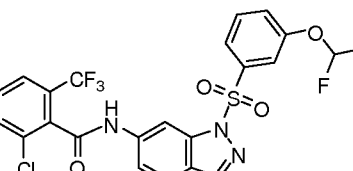
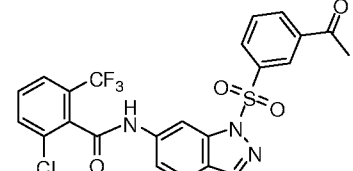
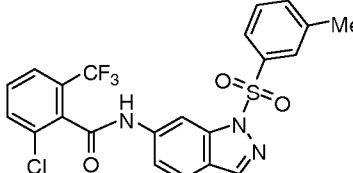
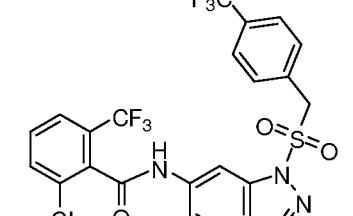
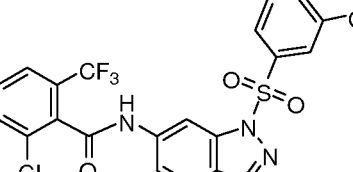
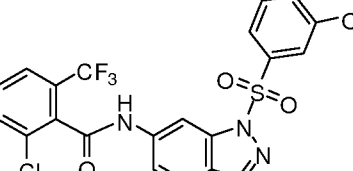
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Compound No.	Chemical Structure
V-20	
V-21	
V-22	
V-23	
V-24	
V-25	
V-26	

- 144 -

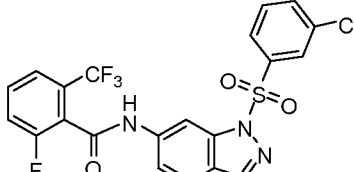
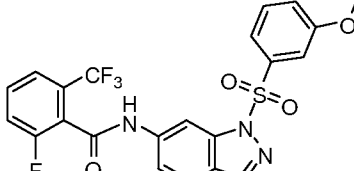
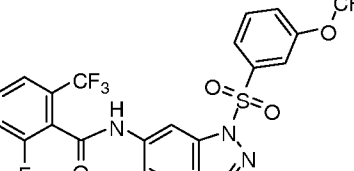
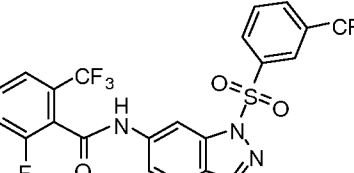
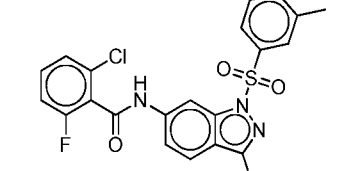
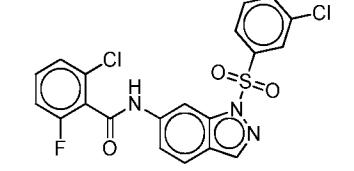
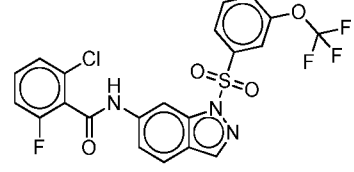
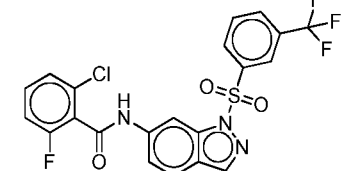
Compound No.	Chemical Structure
V-27	
V-28	
V-29	
V-30	
V-31	
V-32	
V-33	

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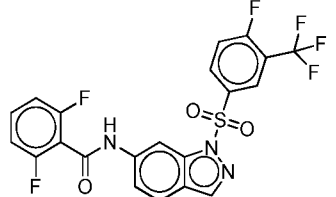
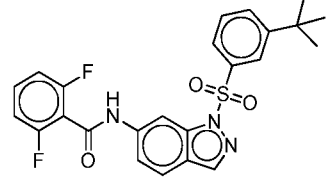
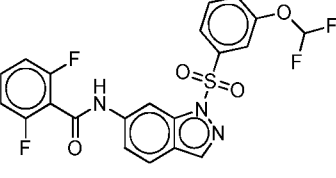
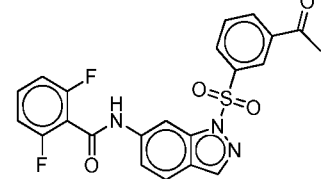
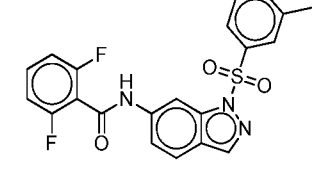
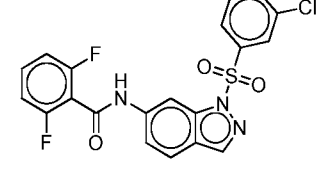
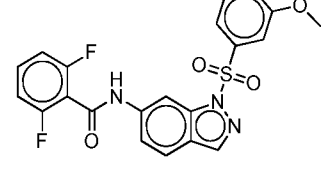
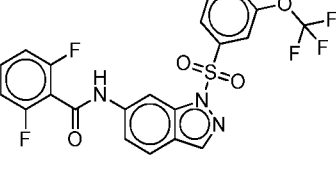
Compound No.	Chemical Structure
V-34	
V-35	
V-36	
V-37	
V-38	
V-39	
V-40	

Compound No.	Chemical Structure
V-41	
V-42	
V-43	
V-44	
V-45	
V-46	
V-47	

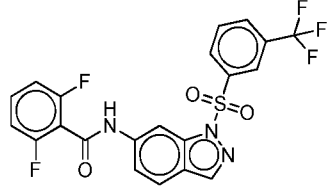
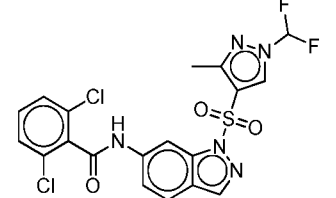
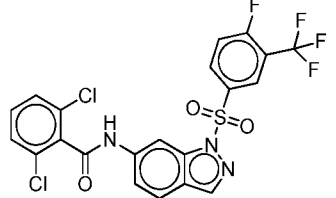
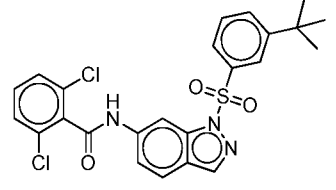
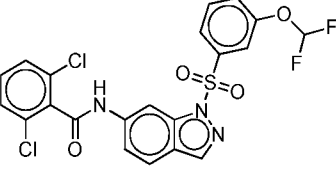
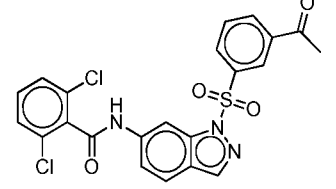
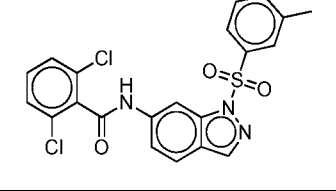
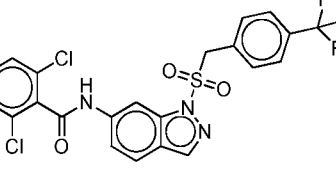
- 147 -

Compound No.	Chemical Structure
V-48	
V-49	
V-50	
V-51	
V-52	
V-53	
V-54	
V-55	

- 148 -

Compound No.	Chemical Structure
V-56	
V-57	
V-58	
V-59	
V-60	
V-61	
V-62	
V-63	

- 149 -

Compound No.	Chemical Structure
V-64	
V-65	
V-66	
V-67	
V-68	
V-69	
V-70	
V-71	

Compound No.	Chemical Structure
V-72	
V-73	
V-74	
V-75	
V-76	
V-77	
V-78	
V-79	

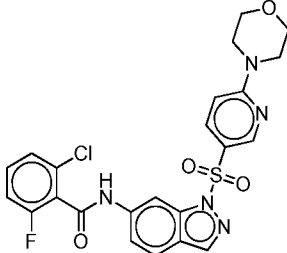
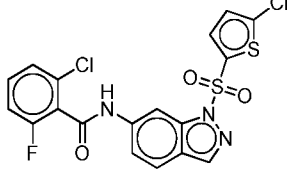
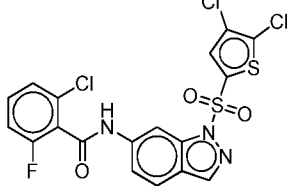
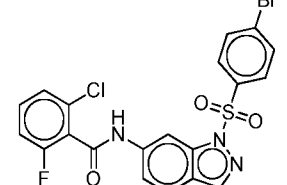
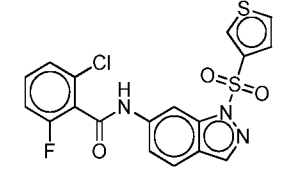
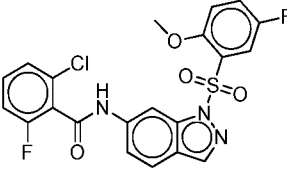
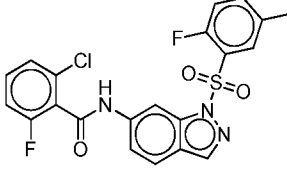
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Compound No.	Chemical Structure
V-80	
V-81	
V-82	
V-83	
V-84	
V-85	
V-86	
V-87	

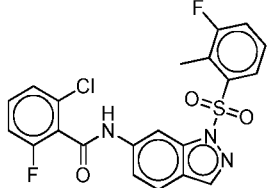
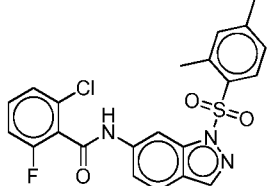
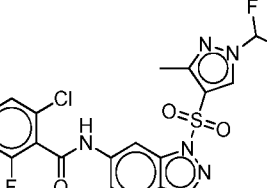
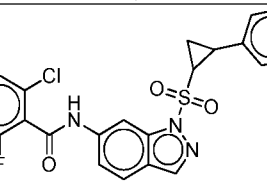
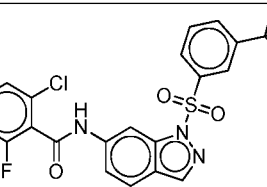
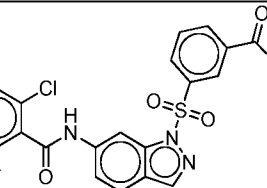
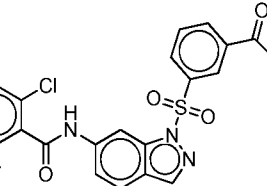
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Compound No.	Chemical Structure
V-88	
V-89	
V-90	
V-91	
V-92	
V-93	
V-94	

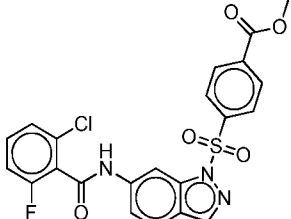
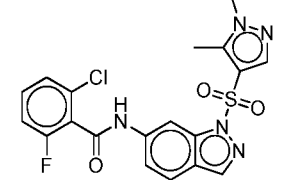
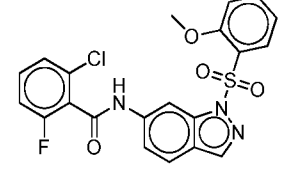
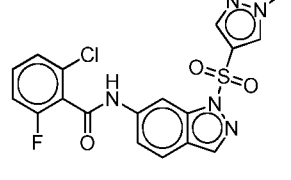
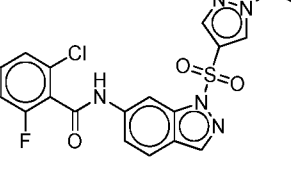
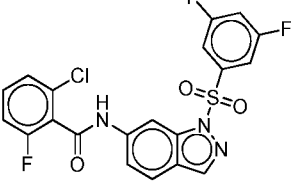
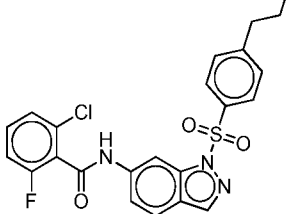
- 153 -

Compound No.	Chemical Structure
V-95	
V-96	
V-97	
V-98	
V-99	
V-100	
V-101	

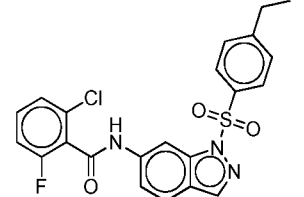
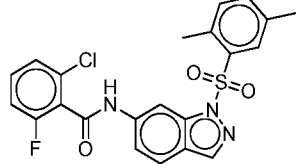
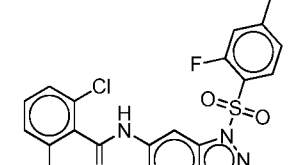
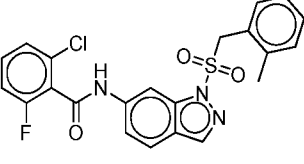
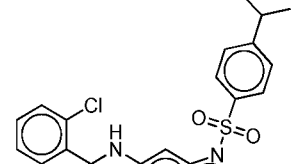
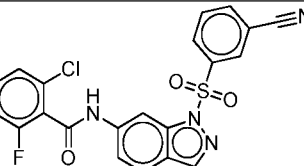
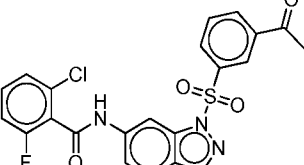
- 154 -

Compound No.	Chemical Structure
V-102	
V-103	
V-104	
V-105	
V-106	
V-107	
V-108	

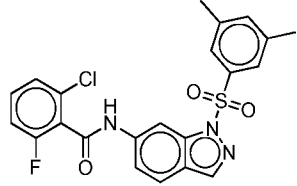
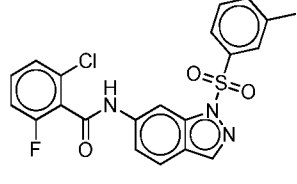
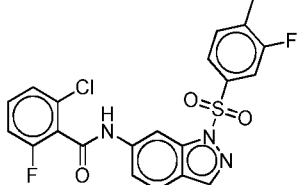
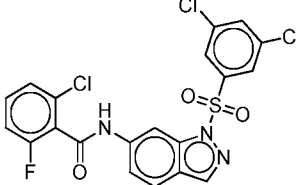
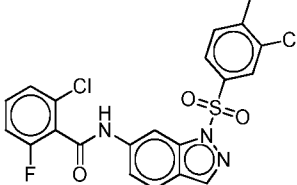
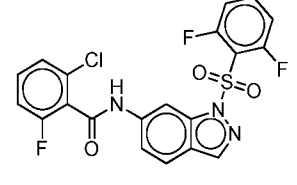
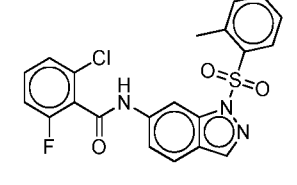
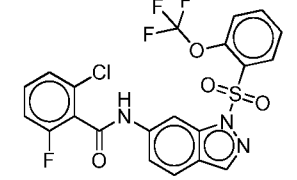
- 155 -

Compound No.	Chemical Structure
V-109	
V-110	
V-111	
V-112	
V-113	
V-114	
V-115	

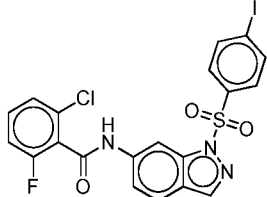
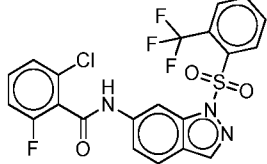
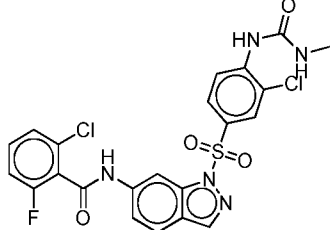
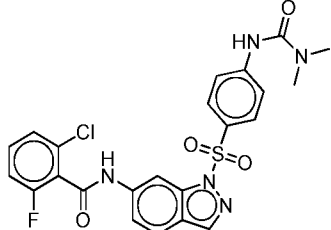
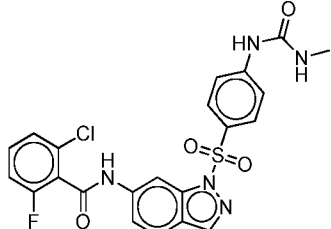
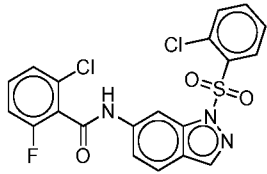
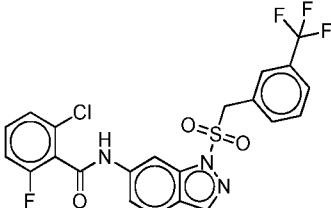
- 156 -

Compound No.	Chemical Structure
V-116	
V-117	
V-118	
V-119	
V-120	
V-121	
V-122	

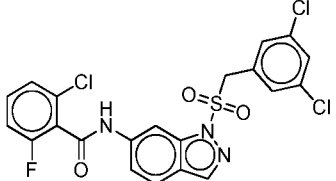
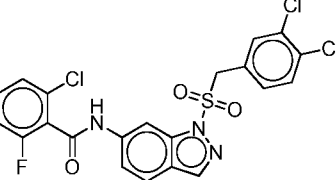
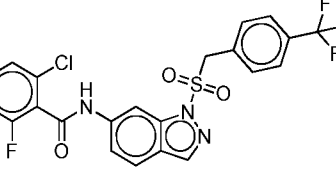
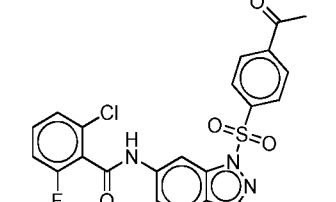
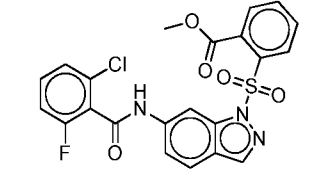
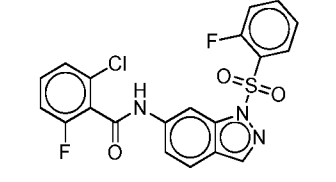
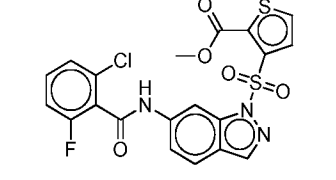
- 157 -

Compound No.	Chemical Structure
V-123	
V-124	
V-125	
V-126	
V-127	
V-128	
V-129	
V-130	

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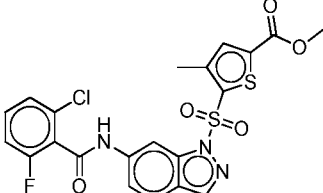
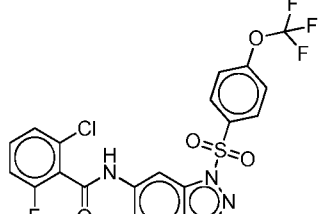
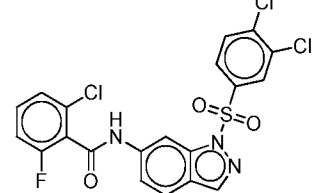
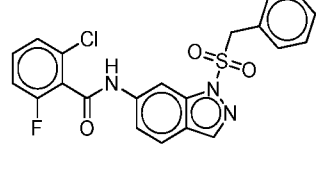
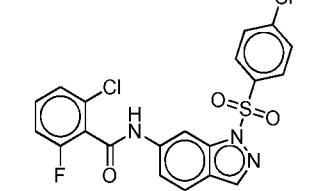
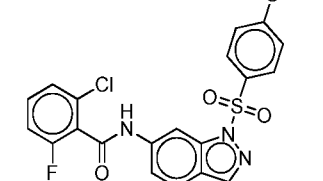
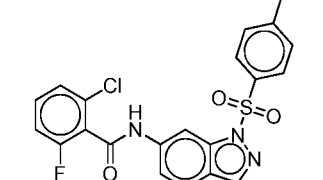
Compound No.	Chemical Structure
V-131	
V-132	
V-133	
V-134	
V-135	
V-136	
V-137	

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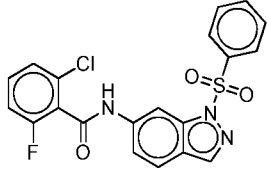
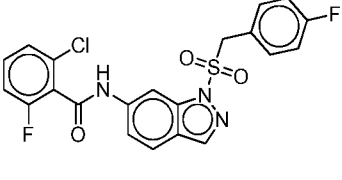
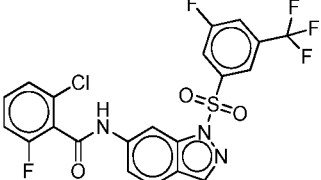
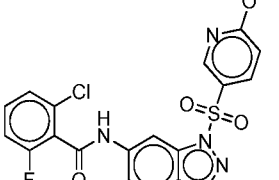
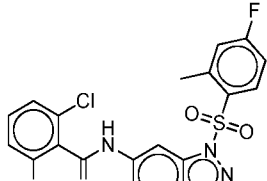
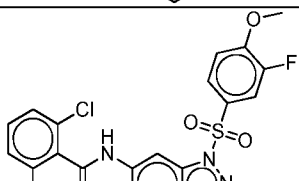
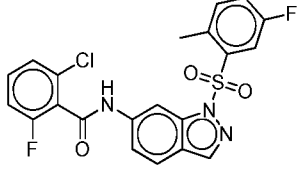
Compound No.	Chemical Structure
V-138	
V-139	
V-140	
V-141	
V-142	
V-143	
V-144	

Compound No.	Chemical Structure
V-145	
V-146	
V-147	
V-148	
V-149	
V-150	
V-151	

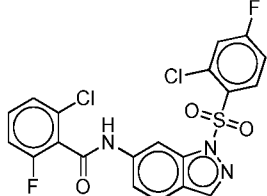
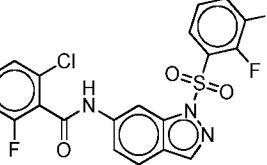
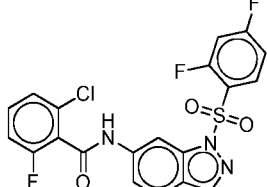
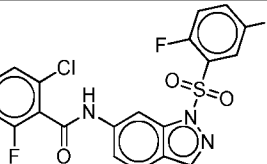
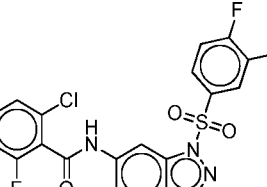
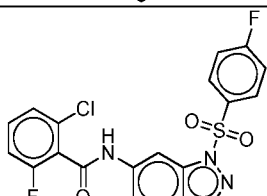
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Compound No.	Chemical Structure
V-152	
V-153	
V-154	
V-155	
V-156	
V-157	
V-158	

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Compound No.	Chemical Structure
V-159	
V-160	
V-161	
V-162	
V-163	
V-164	
V-165	

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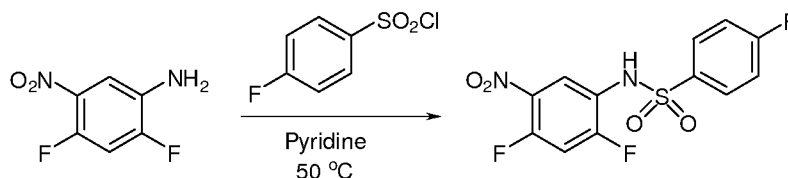
Compound No.	Chemical Structure
V-166	
V-167	
V-168	
V-169	
V-170	
V-171	

EXAMPLE 11 – Preparation of 2-Chloro-6-fluoro-N-[7-fluoro-4-(4-fluorobenzenesulfonyl)-2-methoxymethyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]benzamide (12)

5 [0251] The title compound was prepared according to the procedures described below.

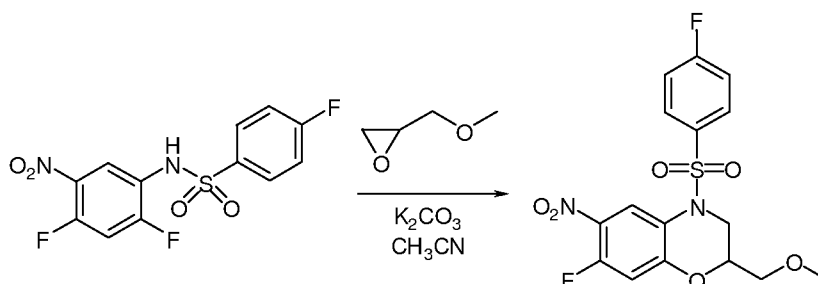
Part I – Synthesis of N-(2,4-Difluoro-5-nitrophenyl)-4-fluorobenzenesulfonamide

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[0252] p-Fluorobenzenesulfonyl chloride (0.52 g, 2.7 mmol) was added to a solution of 2,4-difluoro-5-nitrophenylamine (0.31 g, 1.77 mmol) in pyridine (2 mL). The reaction mixture was stirred at 50 °C for 1 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with 1M HCl and then brine (1 x 10 mL) to provide an organic extract. The organic extract was dried (MgSO₄), concentrated under reduce pressure, and purified by column chromatography (EtOAc/hexanes) to afford N-(2,4-difluoro-5-nitrophenyl)-4-fluorobenzenesulfonamide (0.30 g, 52%). ¹H NMR 250MHz CDCl₃ δ 8.35 (t, J = 7.75 Hz, 1H), 7.83 – 7.89 (m, 2H), 7.16 – 7.23 (m, 2H), 6.97 – 7.05 (m, 1H).

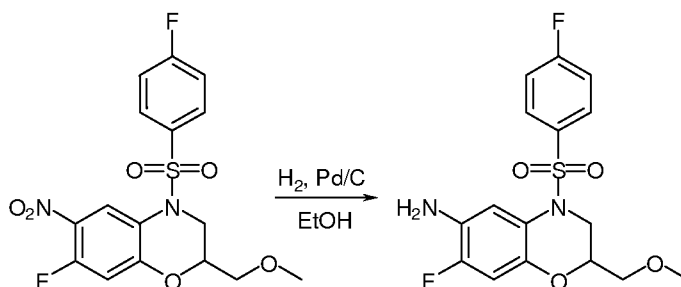
10 **Part II – Synthesis of 7-Fluoro-4-(4-fluorobenzenesulfonyl)-2-methoxymethyl-6-nitro-3,4-dihydro-2H-benzo [1,4]oxazine**



[0253] Glycidyl methyl ether (64 mg, 0.72 mmol) was added to a solution of potassium carbonate (66 mg, 0.48 mmol) and N-(2,4-difluoro-5-nitrophenyl)-4-fluorobenzenesulfonamide (40 mg, 0.12 mmol) in CH₃CN (0.7 mL). The reaction mixture was heated in a microwave reactor at 140 °C for 1 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with H₂O (1 x 10 mL) and brine (1 x 10 mL) to provide an organic extract. The organic extract was dried (MgSO₄) and concentrated under reduced pressure to provide the crude product, which was purified by chromatography (EtOAc/hexanes) to afford 7-fluoro-4-(4-fluorobenzenesulfonyl)-2-methoxymethyl-6-nitro-3,4-dihydro-2H-benzo [1,4]oxazine (20 mg, 42%). ¹H NMR 250MHz CDCl₃ δ 8.62 (d, J = 7.75 Hz, 1H), 7.73 – 7.78 (m, 2H), 7.18 – 7.25 (m, 2H), 6.75 (d, J = 11.5 Hz, 1H), 4.35 (dd, J = 2.5, 14.75 Hz, 1H), 3.66 – 3.72 (m, 1H), 3.51 (dd, J = 2.5, 7.75 Hz, 1H), 3.37 (s, 3H).

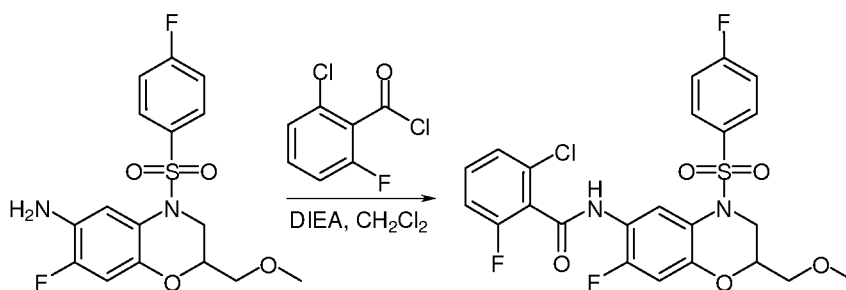
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Part III – Synthesis of 7-Fluoro-4-(4-fluorobenzenesulfonyl)-2-methoxymethyl-3,4-dihydro-2H-benzo[1,4]oxazine-6-ylamine



[0254] 7-Fluoro-4-(4-fluorobenzenesulfonyl)-2-methoxymethyl-6-nitro-3,4-dihydro-2H-benzo [1,4]oxazine (20 mg, 0.05 mmol) and 10% Pd/C (5 mg) were suspended in ethanol (25 mL) and agitated under a hydrogen atmosphere (60 p.s.i.) for 2 h. The reaction mixture was filtered and concentrated under reduced pressure to yield 7-fluoro-4-(4-fluorobenzenesulfonyl)-2-methoxymethyl-3,4-dihydro-2H-benzo[1,4]oxazine-6-ylamine (15 mg, 80%), which was used in the next step without purification. LCMS (ESI): calcd. $C_{16}H_{16}F_2N_2O_4S$, 370.38; found (M+H), 371.

Part IV – Synthesis of 2-Chloro-6-fluoro-N-[7-fluoro-4-(4-fluorobenzenesulfonyl)-2-methoxymethyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]benzamide

**12**

[0255] 2-Chloro-6-fluorobenzoyl chloride (0.02 mL, 0.15 mmol) and diisopropylethylamine (0.05 mL, 0.17 mmol) were added to 7-fluoro-4-(4-fluorobenzenesulfonyl)-2-methoxymethyl-3,4-dihydro-2H-benzo[1,4]oxazine-6-ylamine (15 mg, 0.040 mmol) in CH_2Cl_2 (1 mL). The reaction was stirred at room temperature 1 h and concentrated under reduced pressure. The crude product was purified by HPLC to afford 2-chloro-6-fluoro-N-[7-fluoro-4-(4-fluorobenzenesulfonyl)-2-methoxymethyl-3,4-dihydro-2H-

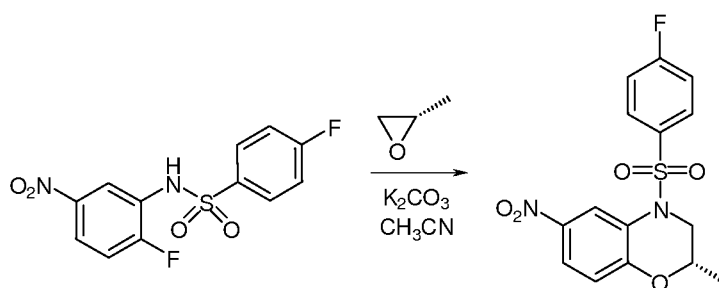
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benzo[1,4]oxazin-6-yl]benzamide. LCMS (ESI): calcd. $C_{23}H_{18}ClF_3N_2O_5S$, 526.92; found (M+H), 527.

EXAMPLE 12 – Preparation of 2-Chloro-6-fluoro-N-[(S)-4-(4-fluorobenzenesulfonyl)-2-methyl-3,4-dihydro-2Hbenzo[1,4]oxazine-6-yl]-benzamide (13)

5 [0256] The title compound was prepared according to the procedures described below.

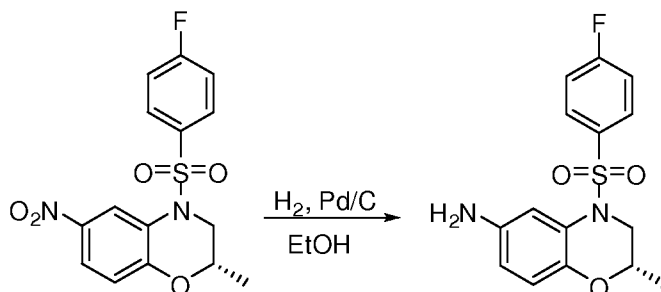
Part I – Synthesis of (S)-4-(4-Fluorobenzenesulfonyl)-2-methyl-6-nitro-3,4-dihydro-2Hbenzo[1,4]oxazine



10 [0257] (S)-Propylene oxide (0.37 mL, 5.3 mmol) was added to a mixture of 4-fluoro-N-(2-fluoro-5-nitrophenyl)-benzenesulfonamide (0.559 g, 1.78 mmol) and potassium carbonate (0.98 g, 7.1 mmol) in CH_3CN (5 mL). The reaction mixture was heated in a microwave reactor at 140 °C for 2 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with H_2O (1 x 10 mL) and brine (1 x 10 mL), dried ($MgSO_4$), and concentrated under reduced pressure to provide the crude product, which was purified by chromatography (EtOAc/hexanes) to yield

15 (S)-4-(4-fluorobenzenesulfonyl)-2-methyl-6-nitro-3,4-dihydro-2Hbenzo[1,4]oxazine (0.32 g, 51%). 1H NMR 250MHz $CDCl_3$ δ 8.73 (d, J = 2.75 Hz, 1H), 7.96 (dd, J = 2.5, 9.0 Hz, 1H), 7.74 – 7.79 (m, 2H), 7.15 – 7.23 (m, 2H), 6.90 (d, J = 9.0 Hz, 1H), 4.30 (dd, J = 2.25, 14.25 Hz, 1H), 3.72 – 3.80 (m, 1H), 3.13 (dd, J = 9.75, 14.25 Hz, 1H), 1.33 (d, J = 6.35 Hz, 3H).

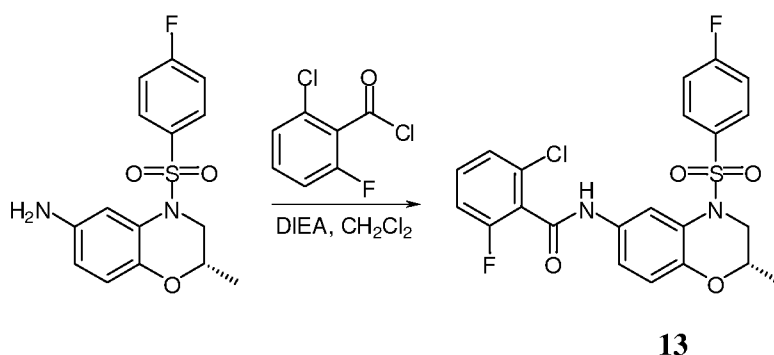
20 **Part II – Synthesis (S)-4-(4-Fluorobenzenesulfonyl)-2-methyl-3,4-dihydro-2Hbenzo[1,4]oxazin-6-ylamine**



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[0258] (S)-4-(4-Fluorobenzenesulfonyl)-2-methyl-6-nitro-3,4-dihydro-2Hbenzo[1,4]oxazine (0.32 g, 0.91 mmol) was hydrogenated over 10% Pd/C (30 mg) at 60 psi in ethanol (50 mL) for 1 h. The reaction mixture was filtered and concentrated under reduced pressure to yield the crude product (0.29 g, 99%). LCMS (ESI): calcd. C₁₅H₁₅FN₂O₃S, 322.36; found (M+H), 323.

Part III – Synthesis 2-Chloro-6-fluoro-N-[(S)-4-(4-fluorobenzenesulfonyl)-2-methyl-3,4-dihydro-2Hbenzo[1,4]oxazine-6-yl]-benzamide



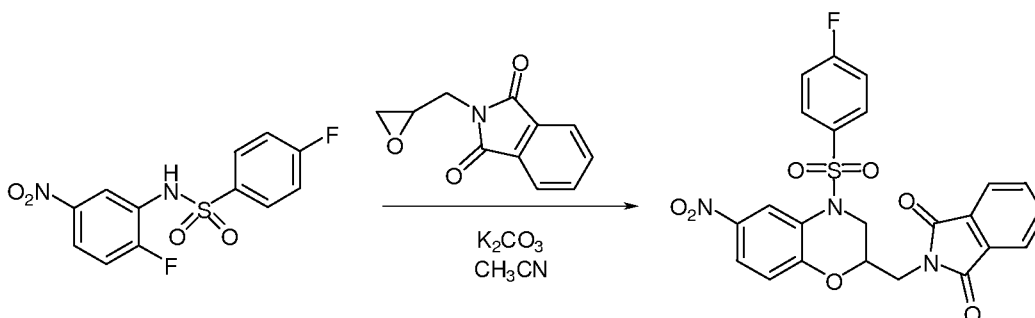
[0259] 2-Chloro-6-fluorobenzoyl chloride was added to a solution of diisopropylethylamine (0.020 mL, 0.15 mmol) and (S)-4-(4-fluorobenzenesulfonyl)-2-methyl-3,4-dihydro-2Hbenzo[1,4]oxazine-6-ylamine (20 mg, 0.062 mmol) in CH₂Cl₂ (1 mL). The reaction mixture was stirred at room temperature for 3 h, and the crude product was purified by HPLC to afford 2-chloro-6-fluoro-N-[(S)-4-(4-fluorobenzenesulfonyl)-2-methyl-3,4-dihydro-2Hbenzo[1,4]oxazine-6-yl]-benzamide. LCMS (ESI): calcd. C₂₂H₁₇ClF₂N₂O₄S, 478.91; found (M+H), 479.

EXAMPLE 13 – Preparation of 2-Chloro-6-fluoro-N-[4-(4-fluorobenzenesulfonyl)-2-methylaminomethyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]benzamide (14)

[0260] The title compound was prepared according to the procedures described below.

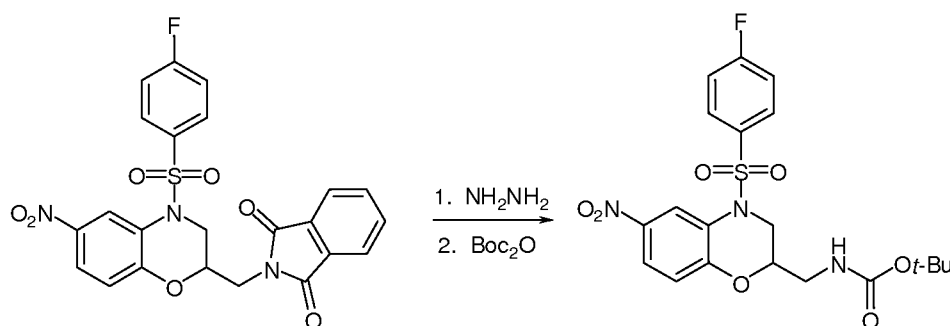
20 Part I – Synthesis of 2-[4-(4-Fluorobenzenesulfonyl)-6-nitro-3,4-dihydro-2H-benzo[1,4]oxazine-2-ylmethyl]isoindole-1,3-dione

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[0261] N-(2,3-Epoxypropyl)phthalimide (3.9 g, 19 mmol) was added to a solution of 4-fluoro-N-(2-fluoro-5-nitrophenyl)-benzenesulfonamide (1.99 g, 6.3 mmol) and potassium carbonate (3.5 g, 25 mmol) in CH₃CN (12 mL). The reaction mixture was heated in a
 5 microwave reactor at 140 °C for 3 h. Then, the reaction mixture was diluted with EtOAc (150 mL) and washed with H₂O (1 x 20 mL) and brine (1 x 10 mL), dried (MgSO₄), and concentrated under reduced pressure to provide the crude product, which was purified by column chromatography (EtOAc/hexanes) to yield 2-[4-(4-fluorobenzenesulfonyl)-6-nitro-3,4-dihydro-2H-benzo[1,4]oxazine-2-ylmethyl]isoindole-1,3-dione (1.30 g, 41%). LCMS (ESI):
 10 calcd. C₂₃H₂₆FN₃O₇S, 497.46; found (M+H+DMSO), 577.

Part II – Synthesis of [4-(4-Fluorobenzenesulfonyl)-6-nitro-3,4-dihydro-2H-benzo[1,4]oxazine-2-ylmethyl]-carbamic acid tert-butyl ester

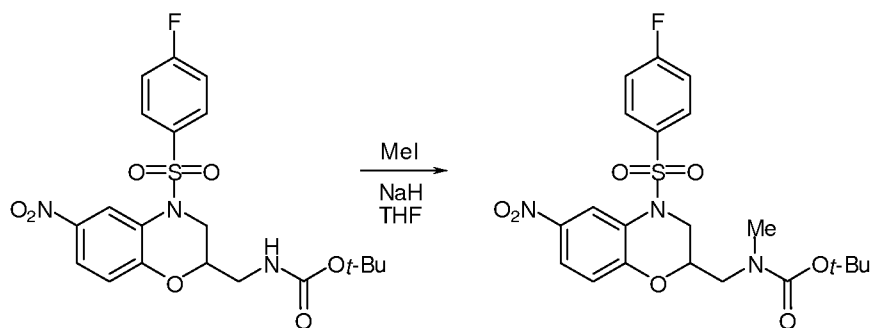


[0262] Hydrazine hydrate (0.38 mL, 7.7 mmol) was added to a solution of 2-[4-(4-fluorobenzene-sulfonyl)-6-nitro-3,4-dihydro-2H-benzo[1,4]oxazine-2-ylmethyl]isoindole-1,3-dione (0.775 g, 1.55 mmol) in methanol (20 mL). The reaction mixture was heated at 80 °C for
 15 30 minutes. Then, the reaction mixture was diluted with EtOAc (100 mL) and washed with H₂O (1 x 20 mL) and brine (1 x 10 mL), dried (MgSO₄), and concentrated under reduced pressure to yield the crude amine.

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[0263] Di-*tert*-butyl dicarbonate (1.0 g, 4.6 mmol) was added to a solution of the crude amine in CH₂Cl₂ (50 mL) and the reaction mixture was stirred at room temperature for 1 h. The crude product was purified by column chromatography (EtOAc/hexanes) to give [4-(4-fluorobenzenesulfonyl)-6-nitro-3,4-dihydro-2H-benzo[1,4]oxazine-2-ylmethyl]-carbamic acid tert-butyl ester (0.481 g, 66%). LCMS (ESI): calcd. C₂₀H₂₂FN₃O₇S, 467.48; found (M+H), 468.

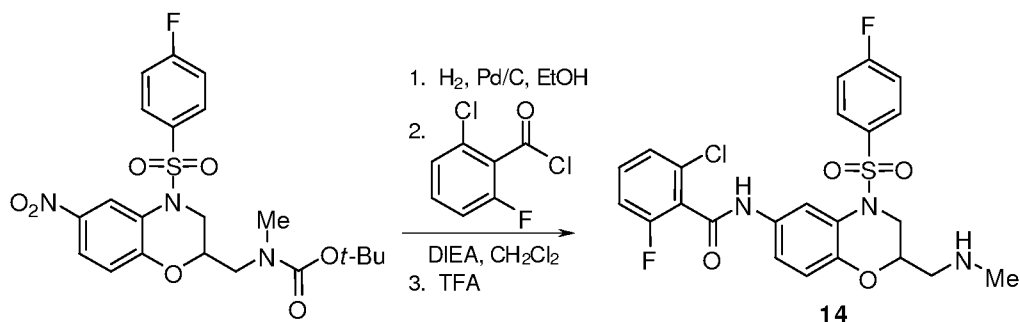
Part III – Synthesis of [4-(4-Fluorobenzenesulfonyl)-6-nitro-3,4-dihydro-2H-benzo[1,4]oxazine-2-ylmethyl]methylcarbamic acid tert-butyl ester



10 [0264] To a solution of [4-(4-fluorobenzenesulfonyl)-6-nitro-3,4-dihydro-2H-benzo[1,4]oxazine-2-ylmethyl]-carbamic acid tert-butyl ester (75 mg, 0.16 mmol) in THF (2 mL) was added methyl iodide (0.05 mL, 0.80 mmol) and sodium hydride (15 mg, 0.38 mmol) in a successive manner. The reaction mixture was stirred at room temperature 1 h. Then, the reaction mixture was diluted with EtOAc (30 mL) and washed with 1M HCl (1 x 5 mL) and
 15 brine (1 x 5 mL), dried (MgSO₄), and concentrated under reduced pressure provide the crude product, which was purified by chromatography (EtOAc/hexanes) to yield [4-(4-fluorobenzenesulfonyl)-6-nitro-3,4-dihydro-2H-benzo[1,4]oxazine-2-ylmethyl]methylcarbamic acid tert-butyl ester (52 mg, 66%). LCMS (ESI): calcd. C₂₁H₂₄FN₃O₇S, 481.50; found (M+H), 482.

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Part IV – Synthesis of 2-Chloro-6-fluoro-N-[4-(4-fluorobenzenesulfonyl)-2-methylaminomethyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]benzamide



[0265] [4-(4-Fluorobenzenesulfonyl)-6-nitro-3,4-dihydro-2H-benzo[1,4]oxazine-2-ylmethyl]methyl-carbamic acid tert-butyl ester (52 mg, 0.11 mmol) was hydrogenated at 60 psi over 10% Pd/C (5 mg) in ethanol (40 mL). The catalyst was removed by filtration and the reaction mixture was concentrated under reduced pressure to yield the crude amine.

[0266] To a solution of the crude amine in CH₂Cl₂ (1 mL) was added 2-chloro-6-fluorobenzoyl chloride (0.02 mL, 0.15 mmol) and DIEA (0.05 mL, 0.17 mmol) and the reaction mixture was stirred at room temperature for 1 h. Then, the reaction mixture was concentrated under reduced pressure to yield the crude amide.

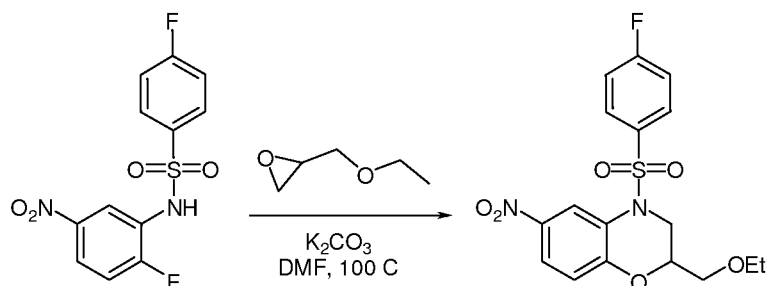
[0267] The crude amide was subjected to trifluoroacetic acid (TFA, 2 mL) at room temperature for 1 h and then the crude product was purified by HPLC to afford 2-chloro-6-fluoro-N-[4-(4-fluorobenzenesulfonyl)-2-methylaminomethyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]benzamide. LCMS (ESI): calcd. C₂₃H₂₀ClF₂N₃O₄S, 507.95; found (M+H), 509.

EXAMPLE 14 – Preparation of 2-Chloro-N-[2-ethoxymethyl-4-(4-fluorobenzenesulfonyl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]-6-trifluoromethyl-benzamide (15)

[0268] The title compound was prepared according to the procedures described below.

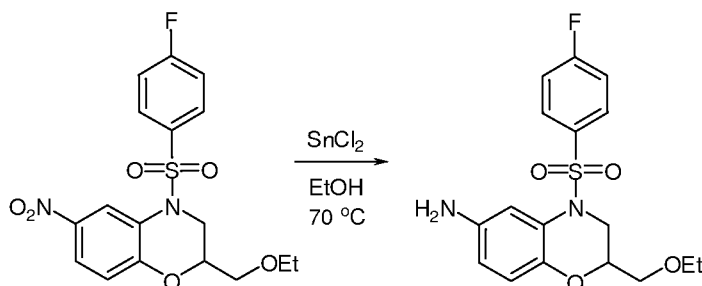
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Part I – Synthesis of 2-Ethoxymethyl-4-(4-fluoro-benzenesulfonyl)-6-nitro-3,4-dihydro-2H-benzo[1,4]oxazine



[0269] 4-Fluoro-N-(2-fluoro-5-nitro-phenyl)-benzenesulfonamide (300 mg, 0.95 mmol),
 5 K_2CO_3 (265 mg, 1.92 mmol), and ethyl glycidyl ether (105 mg, 1.43 mmol) were suspended in
 DMF (2 mL) and heated at 100 °C for 16 h. Upon reaction completion, the solution was
 diluted with EtOAc (10 mL) and H_2O (20 mL). The organic layer was washed with 1M K_2CO_3
 (10 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure to yield 2-
 ethoxymethyl-4-(4-fluoro-benzenesulfonyl)-6-nitro-3,4-dihydro-2H-benzo[1,4]-oxazine (420
 10 mg, 98.9%). LCMS (ESI): calcd. $C_{17}H_{17}FN_2O_6S$, 396; found (M+DMSO+H), 475.

Part II – Synthesis of 2-Ethoxymethyl-4-(4-fluoro-benzenesulfonyl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylamine

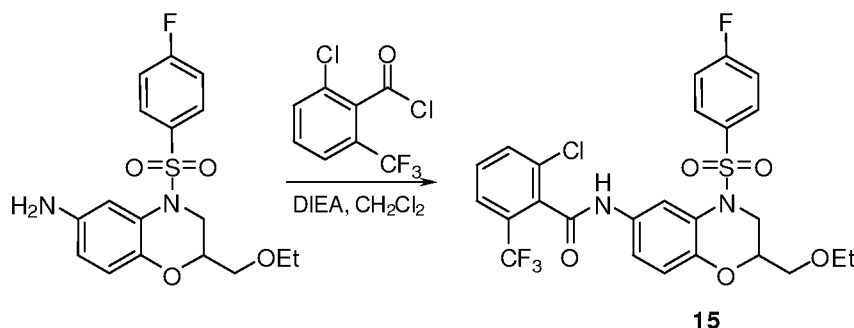


[0270] 2-Ethoxymethyl-4-(4-fluoro-benzenesulfonyl)-6-nitro-3,4-dihydro-2H-
 15 benzo[1,4]oxazine (420 mg, 0.94 mmol) and $SnCl_2 \cdot 2H_2O$ (842 mg, 3.76 mmol) were dissolved
 in EtOH (10 mL) and heated to 70 °C for 16 h. The reaction mixture was cooled to room
 temperature and 2 g of celite was added. The resulting suspension was stirred, and saturated
 $NaHCO_3$ (aq) was added to the vigorously stirring suspension until the pH was basic. Next, the
 mixture was filtered through celite followed by EtOAc washes. The resulting solution was
 20 concentrated under reduced pressure to give 2-ethoxymethyl-4-(4-fluoro-benzenesulfonyl)-3,4-

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dihydro-2H-benzo[1,4]oxazin-6-ylamine (246 mg, 71.5%). LCMS (ESI): calcd. $C_{17}H_{19}FN_2O_4S$, 366; found (M+H), 367.

Part III – Synthesis of 2-Chloro-N-[2-ethoxymethyl-4-(4-fluoro-benzenesulfonyl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]-6-trifluoromethyl-benzamide



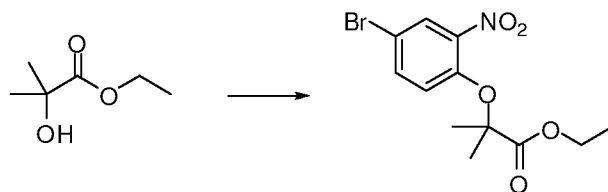
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[0271] To a solution of 2-ethoxymethyl-4-(4-fluoro-benzenesulfonyl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylamine (10 mg, 0.027 mmol) in CH_2Cl_2 (0.300 mL) was added 2-chloro-6-trifluoromethyl-benzoyl chloride (0.0060 mL, 0.032 mmol) and DIEA (0.0055 mL, 0.032 mmol) and the reaction mixture was stirred at room temperature for 30 minutes. Upon reaction completion, the organic solvent was evaporated using a stream of nitrogen and the resulting residue was directly purified by HPLC purification to obtain 2-chloro-N-[2-ethoxymethyl-4-(4-fluoro-benzenesulfonyl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]-6-trifluoromethyl-benzamide (5 mg, 34%). LCMS (ESI): calcd. $C_{25}H_{21}ClF_4N_2O_5S$, 572; found (M+H), 573.

15 **EXAMPLE 15 – Preparation of 2-Chloro-6-fluoro-N-(4-((4-fluorophenyl)sulfonyl)-2,2-dimethyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)benzamide (16)**

[0272] The title compound was prepared according to the procedures described below.

Part I – Synthesis of Ethyl 2-(4-bromo-2-nitrophenoxy)-2-methylpropanoate

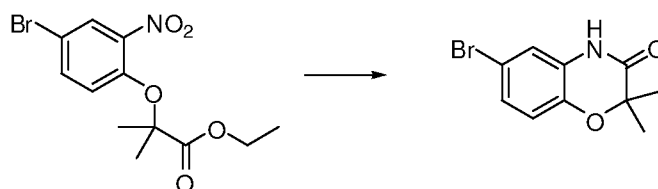


20 [0273] To ethyl 2-hydroxyisobutyrate (2.74 mL, 20.5 mmol) in anhydrous tetrahydrofuran (40 mL) at 0°C was added 15-crown-5 (54 μ L, 0.27 mmol) followed by the portionwise addition of 60% sodium hydride in mineral oil (0.82 g, 20.5 mmol). The reaction mixture was stirred at 0°C for 10 minutes then a solution of 1-bromo-4-fluoro-3-nitrobenzene (3.0 g, 13.6

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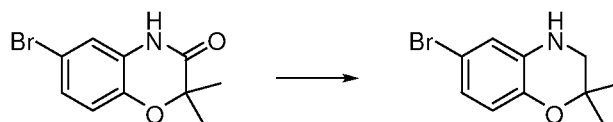
mmol) in anhydrous tetrahydrofuran (10 mL) was added. Next, the reaction mixture was stirred at 0°C for 2 hours, then allowed to warm to ambient temperature. After 1 hour the reaction was quenched with water (100 mL), acidified with 1M hydrogen chloride (25 mL), and extracted with ethyl acetate to provide an organic extract. The organic extract was washed with brine, dried with sodium sulfate, filtered and concentrated *in vacuo* to provide the crude product, which was purified by column chromatography (eluting with a gradient of 0-20% ethyl acetate in hexanes) to yield the title compound (4.15 g, 92% yield).

Part II – Synthesis of 6-Bromo-2,2-dimethyl-2H-benzo[b][1,4]oxazin-3(4H)-one



[0274] To a solution of ethyl 2-(4-bromo-2-nitrophenoxy)-2-methylpropanoate (4.15 g, 12.5 mmol) in acetic acid (40 mL) was added powdered iron (3.5 g, 62.5 mmol) and the resulting mixture was stirred at 70°C for 5 hours. Next, the suspension was cooled, and then filtered through celite washing with ethyl acetate. The filtrates were washed with water, saturated sodium bicarbonate, brine, dried with sodium sulfate, and filtered and concentrated in the presence of silica to provide the crude product, which was purified by column chromatography (eluting with a gradient of 2-30% ethyl acetate in hexanes) to provide the title compound. (2.46 g, 77% yield).

Part III – Synthesis of 6-Bromo-2,2-dimethyl-3,4-dihydro-2H-benzo[b][1,4]oxazine

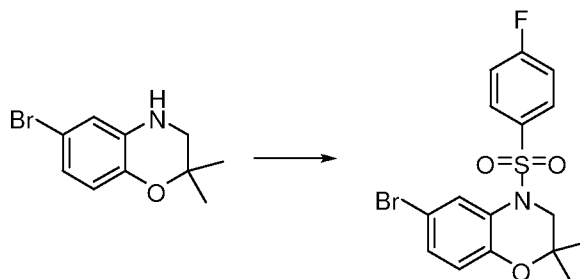


[0275] To a solution of 6-bromo-2,2-dimethyl-2H-benzo[b][1,4]oxazin-3(4H)-one (2.46 g, 9.6 mmol) in anhydrous tetrahydrofuran (40 mL) under a nitrogen atmosphere was added a 10M solution of borane dimethyl sulfide complex in tetrahydrofuran (3.8 mL, 38.4 mmol) slowly. The resulting solution was refluxed for 2 hours. Next, the reaction mixture was cooled to ambient temperature and carefully quenched with the addition of methanol (10 mL). The resulting mixture was heated to reflux for 10 minutes, and then the mixture was cooled and concentrated *in vacuo* to provide the crude product. The crude product was redissolved in ethyl

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acetate, washed with water, brine, dried with sodium sulfate, filtered and concentrated *in vacuo* to yield title compound (2.29 g, 98% yield).

Part IV – Synthesis of 6-Bromo-4-((4-fluorophenyl)sulfonyl)-2,2-dimethyl-3,4-dihydro-2H-benzo[b][1,4]oxazine

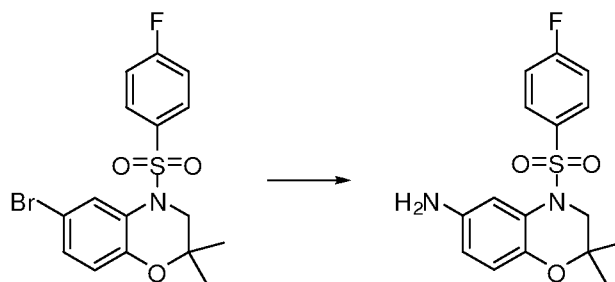


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[0276] To a solution of 6-bromo-2,2-dimethyl-3,4-dihydro-2H-benzo[b][1,4]oxazine (1.7 g, 7.0 mmol) in dichloromethane (15 mL) was added pyridine (1.14 mL, 14.0 mmol) followed by 4-fluorobenzenesulfonyl chloride (1.64 g, 8.4 mmol). Next, a catalytic amount of 4-(dimethylamino)pyridine (~10 mg) was added to the reaction mixture, and the reaction mixture was stirred at ambient temperature overnight. Then, the reaction mixture was concentrated *in vacuo* to provide a residue, which was redissolved in ethyl acetate, washed with 1M hydrogen chloride, brine, dried with sodium sulfate, filtered and concentrated *in vacuo* to provide the crude product. The crude product was purified by column chromatography (eluting with a gradient of 0-30% ethyl acetate in hexanes) to provide the title compound (2.05 g, 73% yield).

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15 Part V – Synthesis of 4-((4-Fluorophenyl)sulfonyl)-2,2-dimethyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-amine



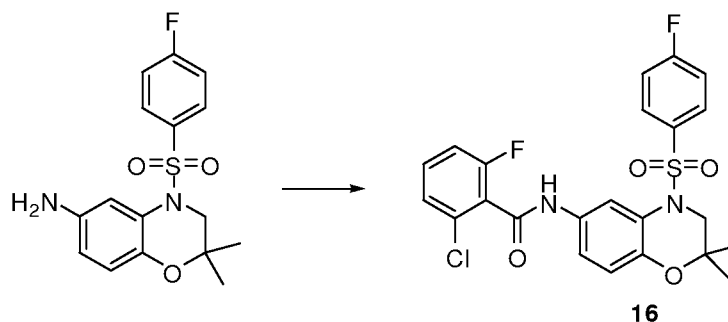
[0277] A suspension of 6-bromo-4-((4-fluorophenyl)sulfonyl)-2,2-dimethyl-3,4-dihydro-2H-benzo[b][1,4]oxazine (2.05 g, 5.1 mmol), benzophenone imine (1.1 g, 6.2 mmol), cesium carbonate (2.5 g, 7.7 mmol), and 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (0.12 g, 0.26 mmol) in anhydrous 1,4-dioxane (24 mL) was evacuated under vacuum and refilled

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with nitrogen three times. To the reaction flask was added tris(dibenzylideneacetone)dipalladium(0) (0.23 g, 0.26 mmol), then the reaction vessel was purged again. Next, the reaction mixture was heated to 110°C for 4 hours. The reaction mixture was cooled, diluted with ethyl acetate, washed with water, brine, dried with sodium sulfate, filtered and concentrated *in vacuo*. The resulting mixture was dissolved in tetrahydrofuran (30 mL), 6M hydrogen chloride (15 mL) was added to produce a mixture that was stirred at ambient temperature for 1 hour, then at 50°C for 1 hour. Next, the mixture mixture was cooled, diluted with ethyl acetate, washed carefully with sat. sodium bicarbonate, brine, dried with sodium sulfate, filtered and concentrated *in vacuo* to provide the crude product, which was purified by column chromatography (eluting with a gradient of 10-70% ethyl acetate in hexanes) to provide the title compound (0.97 g, 56% yield).

Part VI – Synthesis of 2-Chloro-6-fluoro-N-(4-((4-fluorophenyl)sulfonyl)-2,2-dimethyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)benzamide

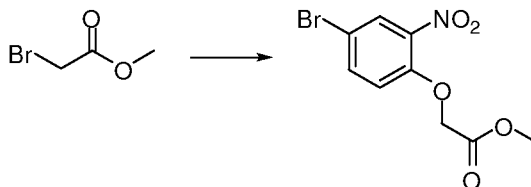


[0278] To a solution of 4-((4-fluorophenyl)sulfonyl)-2,2-dimethyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-amine (215 mg, 0.64 mmol) in tetrahydrofuran (1 mL) was added *N,N*-diisopropylethylamine (0.22 mL, 1.3 mmol) followed by the addition of 2-fluoro-6-chlorobenzoyl chloride (0.1 mL, 0.77 mmol). The reaction mixture was shaken at ambient temperature for 1 hour. Then, the reaction mixture was diluted with ethyl acetate, washed with 1M hydrogen chloride, brine, dried with sodium sulfate, filtered and concentrated *in vacuo* to provide the crude product, which was purified by column chromatography (eluting with a gradient of ethyl acetate in hexanes) to provide the title compound (167 mg, 53% yield). ESI *m/z* 514.97, 516.94 ($M+Na+H$). 1H NMR (400 MHz, DMSO- d_6) δ 10.65 (s, 1H), 8.09 (m, 3H), 7.52 (m, 1H), 7.45 (m, 3H), 7.36 (m, 1H), 7.22 (m, 1H), 6.79 (d, 1H), 3.75 (s, 2H), 1.27 (s, 6H).

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EXAMPLE 16 – Preparation of 2-Chloro-6-fluoro-N-(4-((4-fluorophenyl)sulfonyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)benzamide (17)

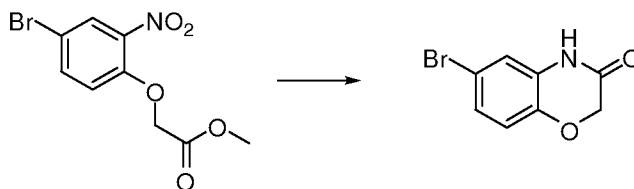
[0279] The title compound was prepared according to the procedures described below.

Part I – Synthesis of Methyl 2-(4-bromo-2-nitrophenoxy)acetate

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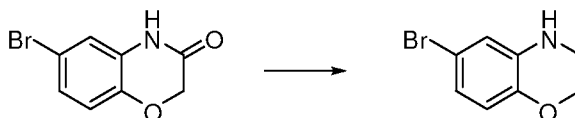
[0280] To a flask containing acetone (20 mL) was sequentially added 4-bromo-2-nitrophenol (1 g, 4.6 mmol), potassium carbonate (0.76 g, 5.5 mmol), and methyl bromoacetate (0.47 mL, 5.1 mmol). The resulting mixture was refluxed overnight, and then the mixture was cooled, partitioned between ethyl acetate and water, separated, washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, filtered and concentrated *in vacuo* to yield title compound. The compound was used in Part II below further without purification. (1.3 g, 100% yield).

10

Part II – Synthesis of 6-Bromo-2H-benzo[b][1,4]oxazin-3(4H)-one

[0281] To a solution of methyl 2-(4-bromo-2-nitrophenoxy)acetate (1.3 g, 4.5 mmol) in acetic acid (15 mL) was added powdered iron (1.25 g, 22.4 mmol). The resulting mixture was stirred at 60°C for 4 hours, then the mixture was cooled. Next, the mixture was filtered through celite, washing with ethyl acetate. The filtrates were washed with water, saturated sodium bicarbonate, brine, dried with sodium sulfate, filtered and concentrated *in vacuo* to provide the crude product, which was purified by column chromatography (eluting with a gradient of 20-100% ethyl acetate in hexane) to provide the title compound (0.79 g, 77% yield).

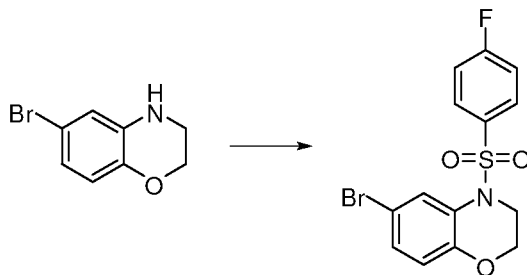
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Part III – Synthesis of 6-Bromo-3,4-dihydro-2H-benzo[b][1,4]oxazine

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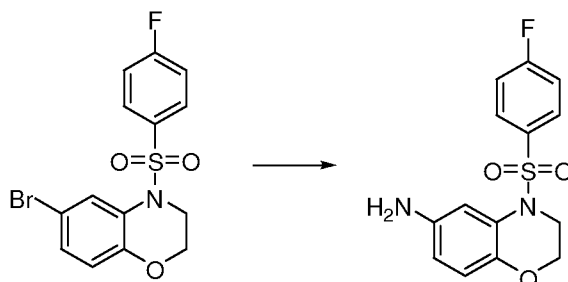
[0282] To a solution of 6-bromo-2H-benzo[b][1,4]oxazin-3(4H)-one (400 mg, 1.75 mmol) in anhydrous tetrahydrofuran (3 mL) under a nitrogen atmosphere was added a 1M solution of borane dimethyl sulfide complex in tetrahydrofuran (7.0 mL, 7.0 mmol) slowly. The resulting solution was refluxed for 3 hours. Then, the reaction mixture was cooled to ambient
5 temperature and carefully quenched with the addition of methanol (10 mL). Next, the reaction mixture was heated to reflux for 10 minutes, and then the reaction mixture was cooled and concentrated *in vacuo* to provide a residue. The residue was redissolved in ethyl acetate, washed with water, brine, dried with sodium sulfate, filtered and concentrated *in vacuo* to yield
10 title compound. The title compound was used in Part IV below without purification. (350 mg, 93% yield) ESI m/z 214.03, 216.0 (M+H).

Part IV – Synthesis of 6-Bromo-4-((4-fluorophenyl)sulfonyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine



[0283] To a solution of 6-bromo-3,4-dihydro-2H-benzo[b][1,4]oxazine (350 mg, 1.6 mmol) in dichloromethane (5 mL) was added pyridine (0.53 mL, 6.5 mmol) followed by 4-fluorobenzenesulfonyl chloride (0.38 g, 2.0 mmol). The reaction mixture was stirred at ambient temperature for 4 hours. Then, the reaction mixture was concentrated *in vacuo* to provide a residue, which was redissolved in ethyl acetate, washed with 1M hydrogen chloride, brine, dried with sodium sulfate, filtered and concentrated *in vacuo* to provide the crude
15 product. The crude product was purified by column chromatography (eluting with a gradient of 0-30% ethyl acetate in hexanes) to provide the title compound (0.49 g, 81% yield).
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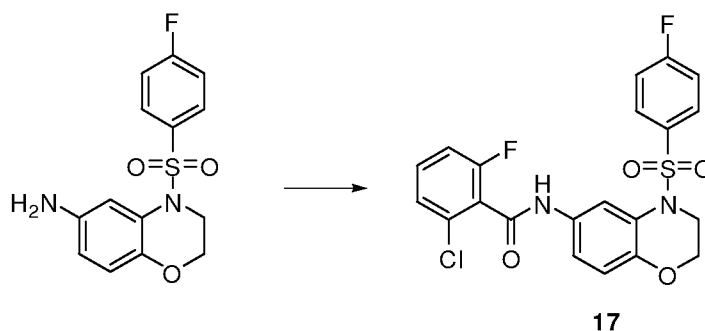
Part V – Synthesis of 4-((4-Fluorophenyl)sulfonyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-amine

[0284] To anhydrous 1,4-dioxane (2 mL) under nitrogen was added 6-bromo-4-((4-
5 fluorophenyl)sulfonyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine (100 mg, 0.27 mmol),
benzophenone imine (58 mg, 0.32 mmol), cesium carbonate (131 mg, 0.40 mmol), and 2-
dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (6 mg, 0.01 mmol), followed by
tris(dibenzylideneacetone)dipalladium(0) (12 mg, 0.01 mmol). The reaction mixture was
heated to 100°C for 4 hours. Then, the reaction mixture was cooled, diluted with ethyl acetate,
10 washed with water, brine, dried with sodium sulfate, filtered and concentrated *in vacuo* to
provide the crude imine intermediate compound, which was purified by column
chromatography (eluting with a gradient of 10-70% ethyl acetate in hexanes) to provide the
imine intermediate compound (80 mg) in purified form.

[0285] Next, the imine intermediate compound was dissolved in tetrahydrofuran (2 mL),
15 6M hydrogen chloride (0.14 mL) as added to the mixture of imine intermediate compound and
THF. The reaction mixture was stirred at ambient temperature for 1 hour. Then, the reaction
mixture was cooled, diluted with ethyl acetate, washed with sat. sodium bicarbonate, brine,
dried with sodium sulfate, filtered and concentrated *in vacuo* to yield title compound (52 mg,
63% yield) ESI *m/z* 309.00 (M+H).

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Part VI – Synthesis of 2-Chloro-6-fluoro-*N*-(4-((4-fluorophenyl)sulfonyl)-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-6-yl)benzamide

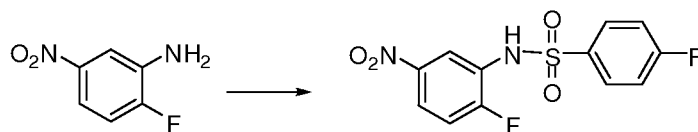


[0286] To a solution of 4-((4-fluorophenyl)sulfonyl)-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-6-amine (52 mg, 0.17 mmol) in tetrahydrofuran (1 mL) was added *N,N*-diisopropylethylamine (59 μ L, 0.34 mmol) followed by the addition of 2-fluoro-6-chlorobenzoyl chloride (27 μ L, 0.20 mmol). The reaction mixture was shaken at ambient temperature for 1 hour. Then, the reaction mixture was diluted with ethyl acetate, washed with 1M hydrogen chloride, brine, dried with sodium sulfate, filtered and concentrated *in vacuo* to provide the crude product. The crude product was purified by column chromatography (eluting with a gradient of ethyl acetate in hexanes) to provide the title compound (43 mg, 54% yield) ESI *m/z* 486.96, 488.96 (M+Na+H); ^1H NMR (400 MHz, DMSO-*d*₆) δ 10.72 (s, 1H), 8.08 (s, 1H), 7.81 (m, 2H), 7.52 (m, 1H), 7.45-7.34 (m, 5H), 6.81 (d, 1H), 3.89 (m, 2H), 3.77 (m, 2H).

EXAMPLE 17 – Preparation of (*R*)-2-Chloro-6-fluoro-*N*-(4-((4-fluorophenyl)sulfonyl)-2-(hydroxymethyl)-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-6-yl)benzamide (18)

[0287] The title compound was prepared according to the procedures described below.

Part I – Synthesis of 4-Fluoro-*N*-(2-fluoro-5-nitrophenyl)benzenesulfonamide



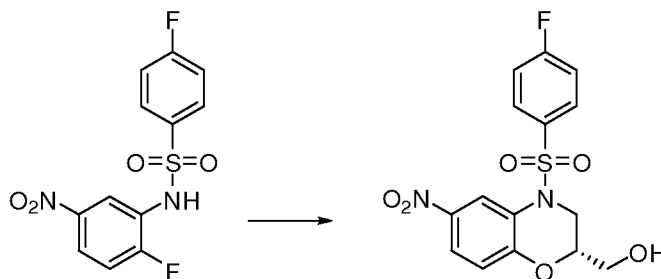
[0288] To a solution of 2-fluoro-5-nitroaniline (10 g, 64 mmol) in anhydrous pyridine (50 mL) under a nitrogen atmosphere was added 4-fluorobenzenesulfonyl chloride (13 g, 67 mmol) and the reaction mixture was heated to 60°C for 4 hours. Next, solvent was mostly removed *in vacuo* from the reaction mixture, and the resulting solution was diluted with ethyl acetate, washed with water, 1M hydrogen chloride, brine, dried with sodium sulfate, filtered and

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concentrated *in vacuo* to yield title compound which was used further without purification (20.1 g, 99% yield).

Part II – Synthesis of (R)-4-((4-Fluorophenyl)sulfonyl)-6-nitro-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanol

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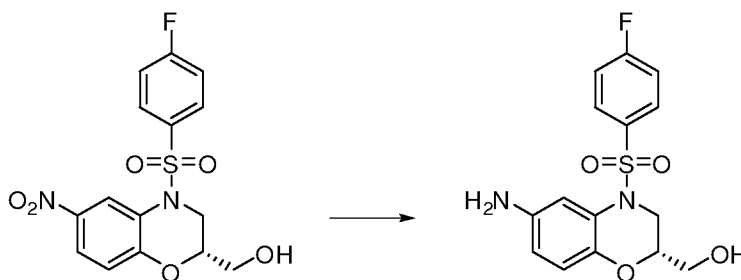


[0289] In three separate microwave tubes was combined 4-fluoro-*N*-(2-fluoro-5-nitrophenyl)benzenesulfonamide (2 g, 6.3 mmol), potassium carbonate (1.3 g, 9.5 mmol) and (*S*)-glycidol (3 mL, 15 mmol) in tetrahydrofuran (15 mL). The resulting mixture was heated in a microwave at 140°C for 2 hours. Next, the three separate, cooled reactions were combined, diluted with ethyl acetate, washed with water, brine, dried with sodium sulfate, filtered and concentrated *in vacuo* to provide the crude product. The crude product was purified by column chromatograph (eluting with a gradient of 20-80% ethyl acetate in hexanes) to provide the title compound (4.6 g, 65% yield).

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Part III – Synthesis of (R)-4-((4-fluorophenyl)sulfonyl)-6-amino-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanol

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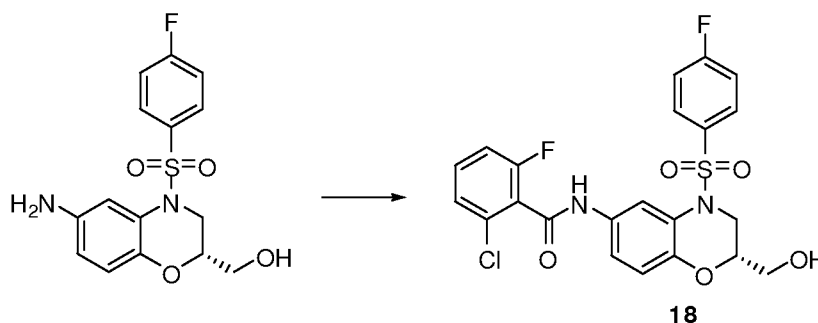
[0290] In a three necked flask equipped with a condenser, a suspension of (R)-4-((4-fluorophenyl)sulfonyl)-6-nitro-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanol (4.6 g, 12.5 mmol) and ammonium formate (3.9 g, 62.4 mmol) in methanol (40 mL) and tetrahydrofuran (10 mL) under a nitrogen atmosphere was evacuated under vacuum and refilled with nitrogen three times before adding 10% palladium on carbon (700 mg). The resulting suspension was refluxed for 1 hour then cooled to ambient temperature. Next, the suspension was filtered

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through celite, and concentrated *in vacuo* to provide a concentrate. The concentrate was then partitioned between ethyl acetate and brine, dried with sodium sulfate, filtered and concentrated *in vacuo* to yield the title compound which was used further without purification (4.1 g, 97% yield).

5 **Part IV – Synthesis of (*R*)-2-Chloro-6-fluoro-*N*-(4-((4-fluorophenyl)sulfonyl)-2-(hydroxymethyl)-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-6-yl)benzamide**



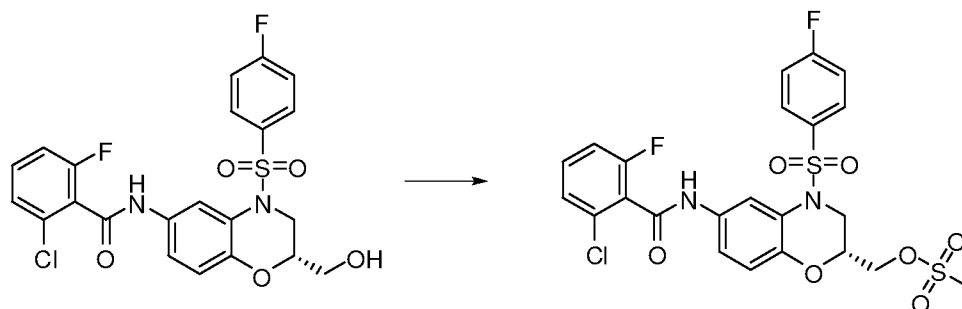
[0291] To a solution of (*R*)-(6-amino-4-((4-fluorophenyl)sulfonyl)-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-2-yl)methanol (3.9 g, 11.5 mmol) in dichloromethane (40 mL) was added pyridine (0.98 mL, 12.1 mmol), cooled to 0°C, then added 2-chloro-6-fluorobenzoyl chloride (1.5 mL, 11.5 mmol) dropwise. Next, the cooling bath was removed and the reaction mixture was stirred at ambient temperature for 30 minutes. Then, the reaction mixture was concentrated *in vacuo* to provide a concentrate, which was diluted with ethyl acetate, washed with 1M hydrogen chloride, brine, dried with sodium sulfate, filtered, and concentrated *in vacuo* to provide the crude product. The crude product was purified by column chromatography (eluting with a gradient of 0.5-3% methanol in dichloromethane) to provide the title compound (5.2 g, 91% yield). ESI *m/z* 516.97, 518.92 (M+Na+H). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.74 (s, 1H), 8.09 (s, 1H), 7.80 (m, 2H), 7.53 (m, 1H), 7.45-7.34 (m, 5H), 6.83 (d, 1H), 5.04 (br m, 1H), 4.3 (m, 1H), 3.55-3.3 (m, 4H).

20 **EXAMPLE 18 – Preparation of (*S*)-2-Chloro-*N*-(2-(cyanomethyl)-4-((4-fluorophenyl)sulfonyl)-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-6-yl)-6-fluorobenzamide (19)**

[0292] The title compound was prepared according to the procedures described below.

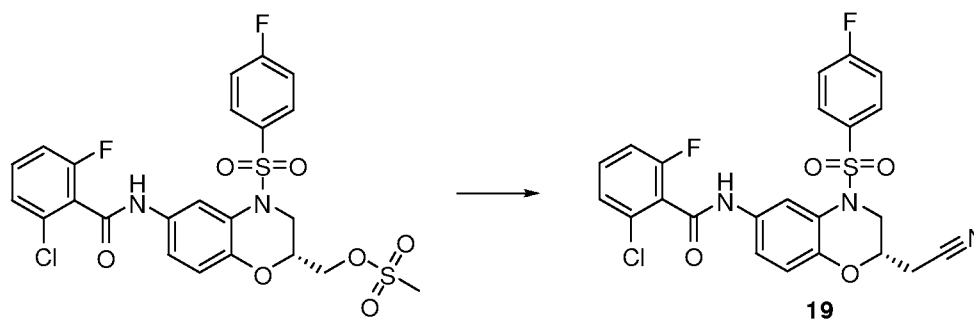
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Part I – Synthesis of (*R*)-(6-(2-Chloro-6-fluorobenzamido)-4-((4-fluorophenyl)sulfonyl)-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-2-yl)methyl methanesulfonate



- [0293]** To (*R*)-2-chloro-6-fluoro-*N*-(4-((4-fluorophenyl)sulfonyl)-2-(hydroxymethyl)-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-6-yl)benzamide (300 mg, 0.61 mmol) in dichloromethane (5 mL) at 0°C was added *N,N*-diisopropylethylamine (0.21 mL, 1.2 mmol) followed by methanesulfonic anhydride (158 mg, 0.91 mmol). Next, the cooling bath was removed and the reaction mixture was stirred at ambient temperature overnight. Then, the reaction mixture was diluted with ethyl acetate, washed with 1M hydrogen chloride, brine, dried with sodium sulfate, filtered and concentrated *in vacuo* to yield title compound, which was used in the next reaction without further purification (360 mg, quant. yield).

Part II – Synthesis of (*S*)-2-Chloro-*N*-(2-(cyanomethyl)-4-((4-fluorophenyl)sulfonyl)-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-6-yl)-6-fluorobenzamide



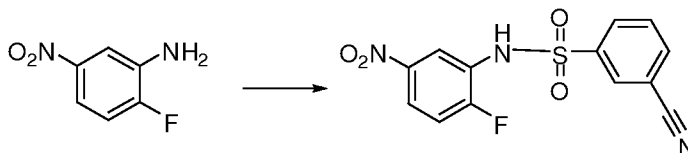
- [0294]** To (*R*)-(6-(2-chloro-6-fluorobenzamido)-4-((4-fluorophenyl)sulfonyl)-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-2-yl)methyl methanesulfonate (50 mg, 0.09 mmol) in *N,N*-dimethylformamide (0.5 mL) was added potassium cyanide (11 mg, 0.17 mmol). The resulting mixture was shaken at 50°C overnight. Then, the reaction mixture was purified by preparatory HPLC to yield the title compound (10 mg, 23% yield).

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EXAMPLE 19 – Preparation of (R)-2-Chloro-N-(4-((3-cyanophenyl)sulfonyl)-2-(hydroxymethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-6-fluorobenzamide (20)

[0295] The title compound was prepared according to the procedures described below.

Part I – Synthesis of 3-Cyano-N-(2-fluoro-5-nitrophenyl)benzenesulfonamide

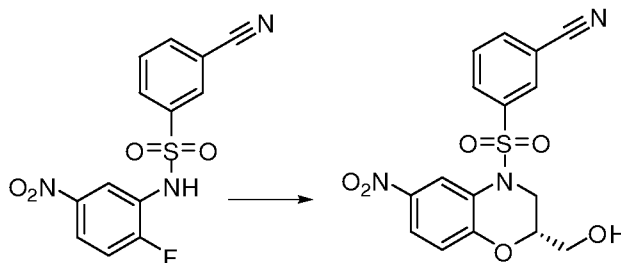


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[0296] To a solution of 2-fluoro-5-nitroaniline (4 g, 25.6 mmol) in anhydrous pyridine (25 mL) under a nitrogen atmosphere was added 3-cyanobenzenesulfonyl chloride (5.7 g, 28.2 mmol). The resulting mixture was heated to 60°C for 4 hours. Then, the solvent was mostly removed *in vacuo*, the resulting oil was diluted with ethyl acetate, washed with water, 1M hydrogen chloride, brine, dried with sodium sulfate, filtered and concentrated *in vacuo* to yield title compound which was used further without purification (7.16 g, 87% yield).

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Part II – Synthesis of (R)-3-((2-(Hydroxymethyl)-6-nitro-2H-benzo[b][1,4]oxazin-4(3H)-yl)sulfonyl)benzonitrile.



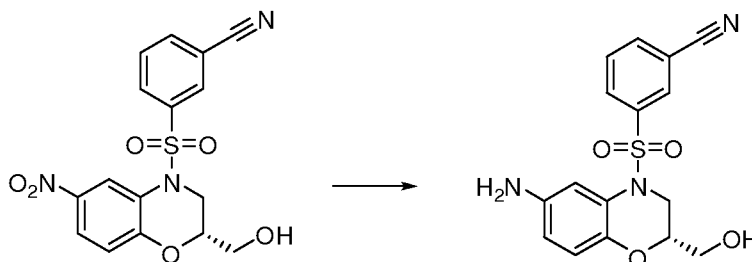
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[0297] In two separate microwave tubes was combined 3-cyano-N-(2-fluoro-5-nitrophenyl)benzenesulfonamide (2 g, 6.2 mmol), potassium carbonate (1.7 g, 12.5 mmol) and (S)-glycidol (1.24 mL, 18.5 mmol) in acetonitrile (8 mL). The reaction mixture was heated in a microwave at 140°C for 40 minutes. Then, the two separate, cooled reactions were combined, diluted with ethyl acetate, washed with water, brine, dried with sodium sulfate, filtered and concentrated *in vacuo* to provide the crude product. The crude product was purified by column chromatography (eluting with a gradient of 30-100% ethyl acetate in hexanes) to provide title compound (1.2 g, 26% yield).

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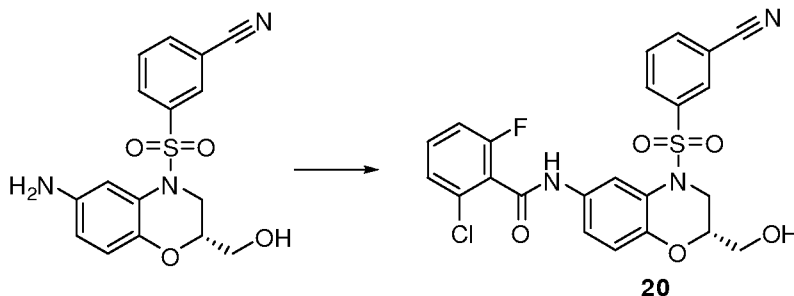
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Part III – Synthesis of (*R*)-3-((6-Amino-2-(hydroxymethyl)-2H-benzo[*b*][1,4]oxazin-4(3H)-yl)sulfonyl)benzonitrile



[0298] In a three-necked flask equipped with a condenser, a suspension of (*R*)-3-((2-(hydroxymethyl)-6-nitro-2H-benzo[*b*][1,4]oxazin-4(3H)-yl)sulfonyl)benzonitrile (440 mg, 1.2 mmol) and ammonium formate (370 mg, 5.9 mmol) in methanol (15 mL) under a nitrogen atmosphere was evacuated under vacuum and refilled with nitrogen three times before adding 10% palladium on carbon (120 mg). The resulting suspension was heated to reflux for 3 hours, and then cooled to ambient temperature. Next, the suspension was filtered through celite, then concentrated *in vacuo* to provide a concentrate. The concentrate was partitioned between ethyl acetate and brine, dried with sodium sulfate, filtered and concentrated *in vacuo* to yield title compound which was used further without purification (320 mg, 79% yield).

Part IV – Synthesis of (*R*)-2-Chloro-*N*-(4-((3-cyanophenyl)sulfonyl)-2-(hydroxymethyl)-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-6-yl)-6-fluorobenzamide



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[0299] To (*R*)-3-((6-amino-2-(hydroxymethyl)-2H-benzo[*b*][1,4]oxazin-4(3H)-yl)sulfonyl)benzonitrile (550 mg, 1.6 mmol) in tetrahydrofuran (10mL) was added *N,N*-diisopropylethylamine (0.28 mL, 1.6 mmol) followed by 2-chloro-6-fluorobenzoyl chloride (0.21 mL, 1.6 mmol). The reaction mixture was stirred at ambient temperature for 1 hour. Then, the reaction mixture was diluted with ethyl acetate, washed with 1M hydrogen chloride, brine, dried with sodium sulfate, filtered and concentrated *in vacuo* to provide the crude product. The crude product was purified twice by column chromatography (eluting with a

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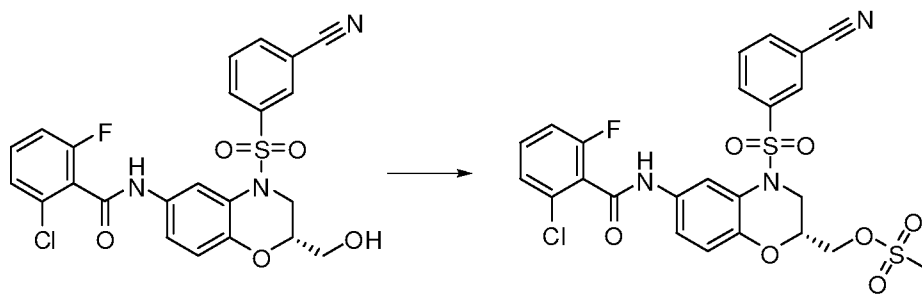
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gradient of ethyl acetate in hexanes) to provide the title compound (305 mg, 38% yield). ESI m/z 523.81, 525.81 (M+Na+H). ^1H NMR (400 MHz, DMSO- d_6) δ 10.73 (s, 1H), 8.30 (s, 1H), 8.16 (m, 1H), 8.11 (s, 1H), 8.04 (m, 1H), 7.78 (m, 1H), 7.52 (m, 1H), 7.43 (m, 1H), 7.36 (m, 2H), 6.84 (d, 1H), 5.05 (m, 1H), 4.34 (m, 1H), 3.6-3.4 (m, 4H).

5 **EXAMPLE 20 – Preparation of (S)-2-Chloro-N-(4-((3-cyanophenyl)sulfonyl)-2-(pyrrolidin-1-ylmethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-6-fluorobenzamide (21)**

[0300] The title compound was prepared according to the procedures described below.

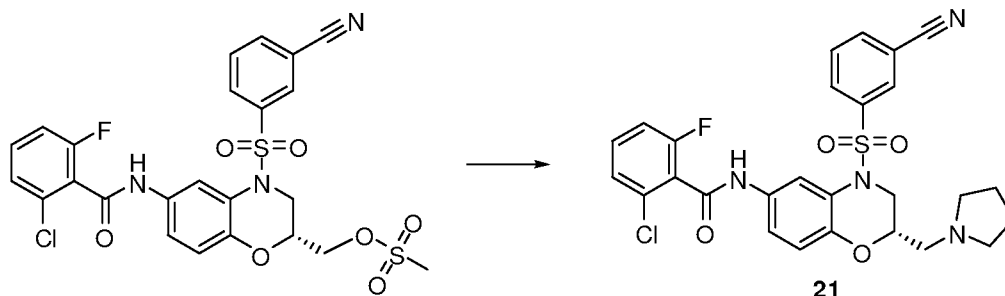
Part 1 – Synthesis of (R)-(6-(2-Chloro-6-fluorobenzamido)-4-((3-cyanophenyl)sulfonyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methyl methanesulfonate



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[0301] To (R)-2-chloro-N-(4-((3-cyanophenyl)sulfonyl)-2-(hydroxymethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-6-fluorobenzamide (100 mg, 0.2 mmol) in dichloromethane (2 mL) was added *N,N*-diisopropylethylamine (52 μL , 0.3 mmol) followed by methanesulfonic anhydride (52 mg, 0.3 mmol). The reaction mixture was stirred reaction at ambient
15 temperature for 2 hours, then diluted with ethyl acetate, washed with 1M hydrogen chloride, brine, dried with sodium sulfate, filtered and concentrated *in vacuo* to yield title compound as a crude mixture. (115 mg, 99% yield).

Part II – Synthesis of (S)-2-Chloro-N-(4-((3-cyanophenyl)sulfonyl)-2-(pyrrolidin-1-ylmethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-6-fluorobenzamide

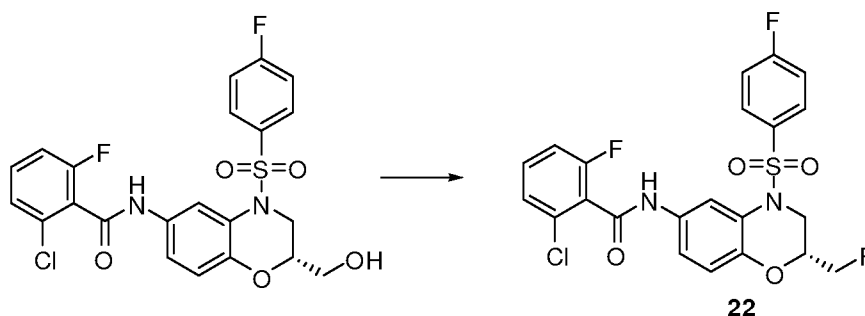


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[0302] To (*R*)-(6-(2-chloro-6-fluorobenzamido)-4-((3-cyanophenyl)sulfonyl)-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-2-yl)methyl methanesulfonate (58 mg, 0.1 mmol) in *N,N*-dimethylformamide (1 mL) was added pyrrolidine (30 μ L, 0.36 mmol). The reaction mixture was stirred at ambient temperature for 1 hour, then the reaction mixture was stirred at 60°C for 5 1 hour. Analytical analysis indicated that a majority of the starting material remained. Therefore, the reaction mixture was stirred at 100 °C for 18 hours. Next, the reaction mixture was concentrated *in vacuo* to provide the crude product, which was purified by preparatory HPLC to yield the title compound (10 mg, 18% yield). ESI *m/z* 554.93, 556.9 (M+H).

EXAMPLE 21 – Preparation of (*R*)-2-Chloro-6-fluoro-*N*-(2-(fluoromethyl)-4-((4-fluorophenyl)sulfonyl)-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-6-yl)benzamide (22)

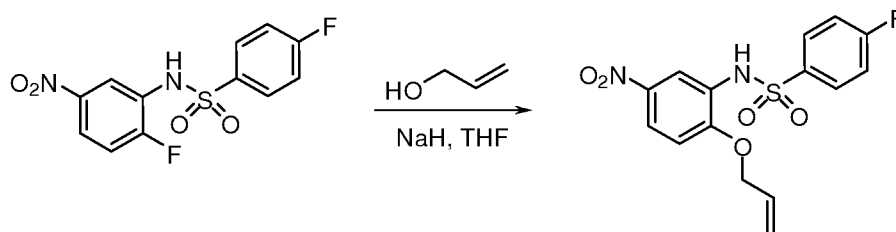


[0303] To (*R*)-2-chloro-6-fluoro-*N*-(4-((4-fluorophenyl)sulfonyl)-2-(hydroxymethyl)-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-6-yl)benzamide (60 mg, 0.12 mmol) in anhydrous dichloromethane (2 mL) under a nitrogen atmosphere at 0°C was added bis-(2-15 methoxyethyl)aminosulfur trifluoride (0.02 mL, 0.12 mmol). Then, the cooling bath was removed and the reaction mixture was stirred at ambient temperature for 1 hour. Next, the reaction mixture was diluted with dichloromethane, washed with brine, dried with sodium sulfate, filtered and concentrated *in vacuo* to provide the crude product. The crude product was purified by column chromatography (eluting with a gradient of ethyl acetate in hexanes) to 20 provide the title compound (16 mg, 27% yield). ESI *m/z* 518.79, 520.80 (M+Na+H). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.76 (s, 1H), 8.11 (s, 1H), 7.85 (m, 2H), 7.53 (m, 1H), 7.46-7.35 (m, 5H), 6.88 (d, 1H), 4.68 (m, 1H), 4.57 (m, 1H), 4.4 (m, 1H), 3.38 (m, 2H).

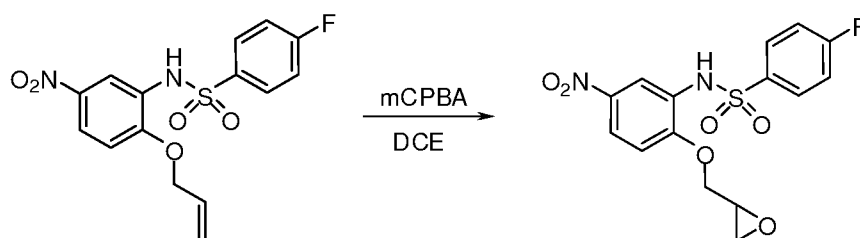
EXAMPLE 22 – Preparation of 2-Chloro-6-fluoro-*N*-[4-(4-fluorobenzenesulfonyl)-3-hydroxymethyl-3,4-dihydro-2H-benzo[1,5]oxazin-6-yl]benzamide (23)

[0304] The title compound was prepared according to the procedures described below.

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Part I – Synthesis of N-2-(Allyloxy-5-nitrophenyl)-4-fluorobenzenesulfonamide

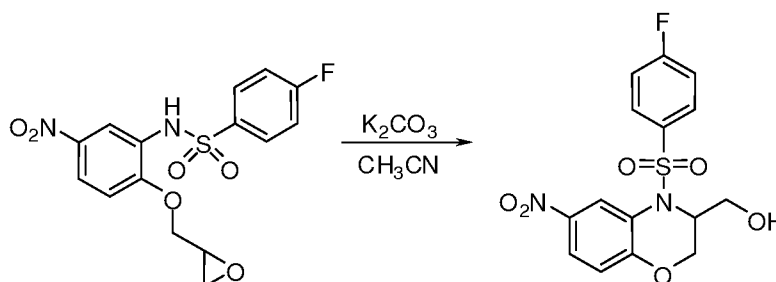
- [0305]** Sodium hydride (0.26 g, 6.6 mmol) was added to allyl alcohol (0.45 mL, 6.6 mmol) in THF (5 mL) and stirred for 3 minutes. 4-Fluoro-N-(2-fluoro-5-nitrophenyl)-
- 5 benzenesulfonamide (0.42 g, 1.3 mmol) was added and the reaction mixture was stirred for 3 hours. The reaction was quenched by adding 1M HCl (10 mL), and then the resulting mixture was extracted with EtOAc (2 x 50 mL). The organic extracts were washed with brine (1 x 10 mL), dried (MgSO₄), and concentrated to provide the crude product, which was purified by chromatography (SiO₂, eluent EtOAc/hexanes) to provide the title compound. Yield = 76 mg
- 10 (16%). ¹H NMR 250MHz CDCl₃ δ 8.39 (d, 1H, J = 3.0 Hz), 7.93 (dd, 1H, J = 2.75, 9.0 Hz), 7.0 – 7.86 (m, 2H), 7.07 – 7.14 (m, 2H), 6.82 (d, 1H, J = 9.0 Hz), 5.80 – 5.92 (m, 1H), 5.22 – 5.34 (m, 2H), 4.52 – 4.55 (m, 2H).

Part II – Synthesis of 4-Fluoro-N-(5-nitro-2-oxiranylmethoxyphenyl)-benzenesulfonamide

- 15 **[0306]** meta-Chloroperoxybenzoic acid (mCPBA; 83 mg, 0.34 mmol) was added to a solution of N-2-(allyloxy-5-nitrophenyl)-4-fluorobenzenesulfonamide (76 mg, 0.22 mmol) in dichloroethane (DCE; 2 mL) and heated at reflux for 30 min. Then, the reaction mixture was diluted with diethyl ether (40 mL) and washed with Na₂S₂O₄ (10 mL), Na₂CO₃ (3 x 10 mL), and brine (10 mL) and concentrated to provide the title compound. Yield = 78 mg (97%).
- 20 LCMS (ESI): calc. C₁₅H₁₃FN₂O₆S = 368.34; obs. M+H = 369.

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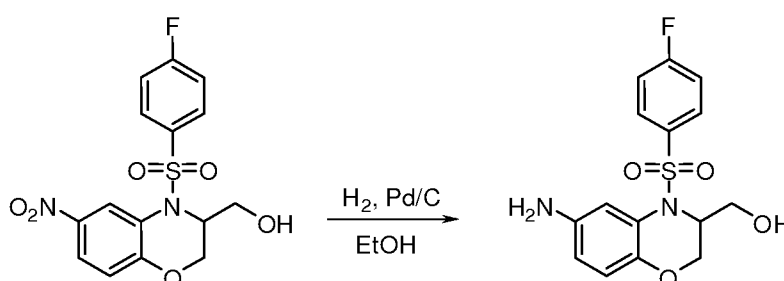
Part III – Synthesis of [4-(4-Fluorobenzenesulfonyl)-6-nitro-3,4-dihydro-2H-benzo[1,4]oxazin-3-yl]methanol



[0307] K_2CO_3 (100 mg, 0.74 mmol) was added to 4-fluoro-N-(5-nitro-2-oxiranylmethoxyphenyl)-benzenesulfonamide (70 mg, 0.19 mmol) in CH_3CN (1.5 mL). The reaction mixture was heated at 140 °C by microwave irradiation for 40 min. Then, the reaction mixture was diluted with EtOAc (50 mL) and washed with water (1 x 10 mL) and brine (1 x 10 mL), dried ($MgSO_4$), and concentrated to provide the title compound. Yield = 47 mg (70%).

1H NMR 250MHz $CDCl_3$ δ 8.81 (d, 1H, $J = 2.75$ Hz), 7.98 (dd, 1H, $J = 2.5, 9.0$ Hz), 7.70 – 7.76 (m, 1H), 7.16 – 7.22 (m, 2H), 6.94 (d, 1H, $J = 9.0$ Hz), 4.35 – 4.50 (m, 1H), 4.39 (dd, 1H, $J = 1.5, 11.5$ Hz), 3.65 – 3.73 (m, 1H), 3.53 (dd, 1H, $J = 7.75$ Hz, 11.25 Hz), 3.36 (dd, 1H, $J = 3.0, 11.25$ Hz).

Part IV – Synthesis of [6-Amino-4-(4-fluorobenzenesulfonyl)-3,4-dihydro-2H-benzo[1,4]oxazin-3-yl]methanol

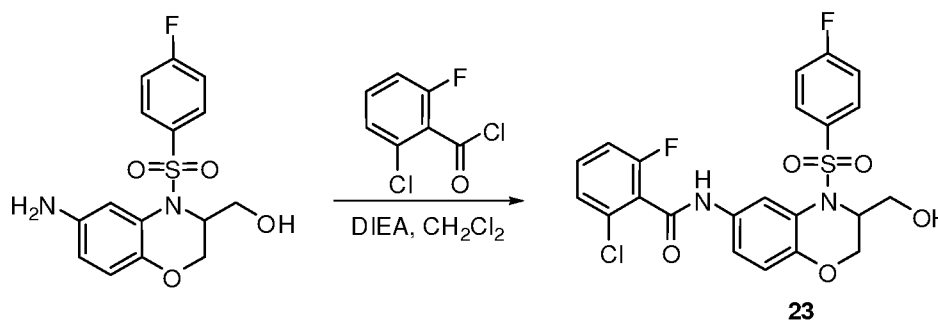


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[0308] [4-(4-Fluorobenzenesulfonyl)-6-nitro-3,4-dihydro-2H-benzo[1,4]oxazin-3-yl]methanol (47 mg, 0.13 mmol) was hydrogenated at 60 psi over 10% Pd/C (5 mg) in ethanol (30 mL) for 45 min. Then, the reaction mixture was filtered and concentrated to provide the title compound. Yield = 24 mg (55%). 1H NMR 250 MHz $CDCl_3$ 7.63 – 7.18 (m, 2H), 7.30 (d, 1H, $J = 2.75$ Hz), 7.09 – 7.16 (m, 2H), 6.62 (d, 1H, $J = 8.75$), 6.67 (dd, 1H, $J = 2.75, 8.75$ Hz), 4.30 – 4.37 (m, 1H), 4.01 – 4.16 (m, 1H), 3.46 – 3.73 (m, 2H), 3.12 (dd, 1H, $J = 3.25, 11.5$ Hz).

20

Part V – Synthesis of 2-Chloro-6-fluoro-N-[4-(4-fluorobenzenesulfonyl)-3-hydroxymethyl-3,4-dihydro-2H-benzo[1,5]oxazin-6-yl]benzamide



[0309] 2-Chloro-6-fluorobenzoyl chloride (0.02 mL, 0.15 mmol) and diisopropylethylamine (DIEA; 0.05 mL, 0.17 mmol) were added to [6-amino-4-(4-fluorobenzenesulfonyl)-3,4-dihydro-2H-benzo[1,4]oxazin-3-yl]methanol (24 mg, 0.071 mmol) in CH₂Cl₂ (1 mL). Then, the reaction mixture was stirred at room temperature for 1 hr and then concentrated to provide the crude product, which was purified by HPLC to provide the title compound. LCMS (ESI): calc. C₂₂H₁₇ClF₂N₂O₅S = 494.90; obs. M+H = 495.

10 **EXAMPLE 23** – Preparation of Additional Benzoxazine Compounds

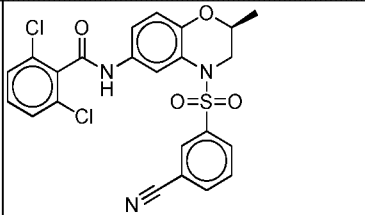
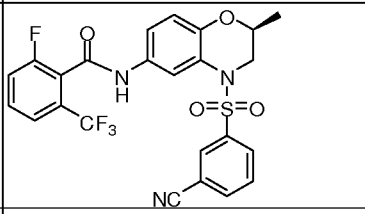
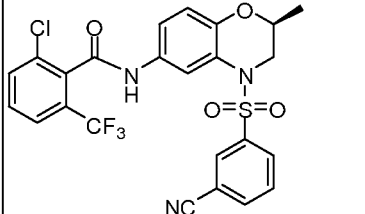
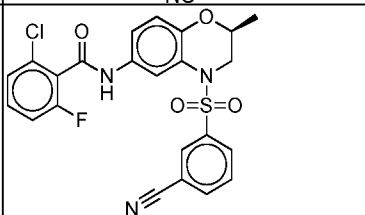
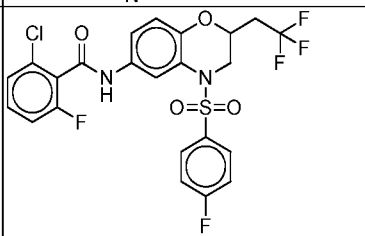
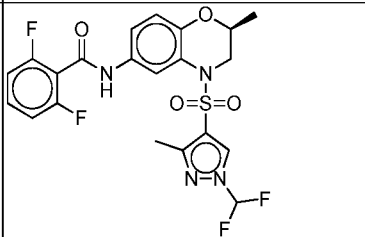
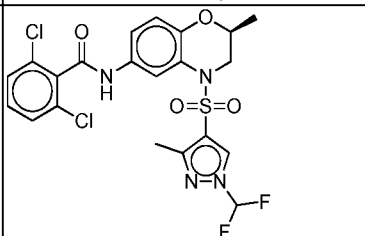
[0310] The compounds in Table 6 below were prepared based on the experimental procedures described in Examples 11-22 and in the detailed description. Starting materials can be obtained from commercial sources or readily prepared from commercially available materials.

15

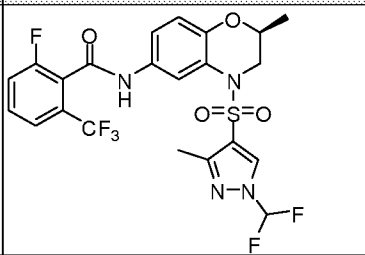
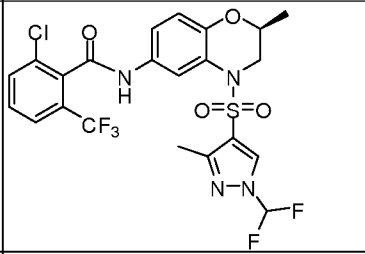
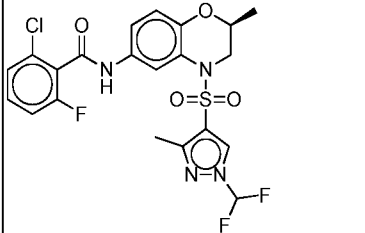
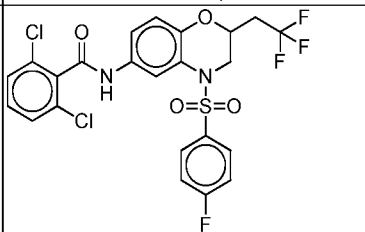
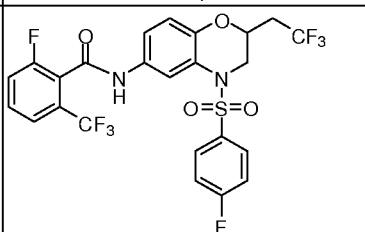
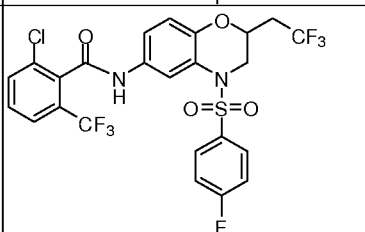
TABLE 6.

Compound No.	Chemical Structure
VI-1	
VI-2	

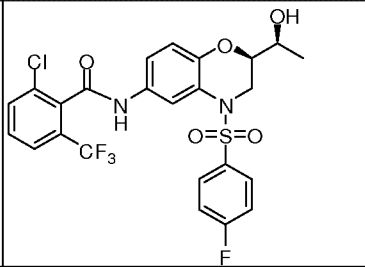
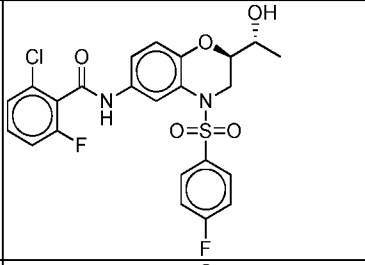
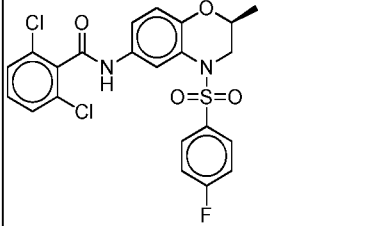
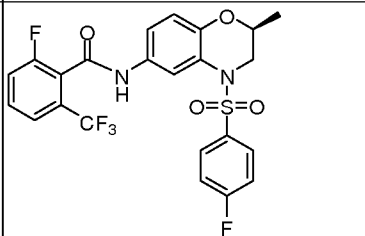
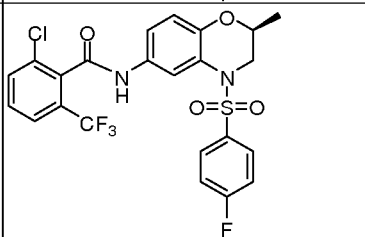
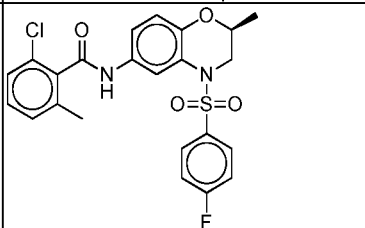
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Compound No.	Chemical Structure
VI-3	
VI-4	
VI-5	
VI-6	
VI-7	
VI-8	
VI-9	

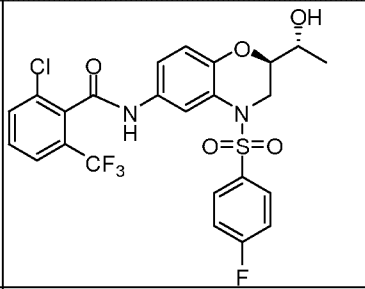
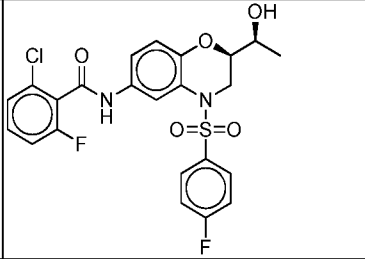
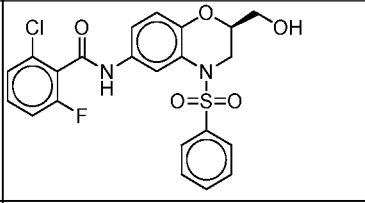
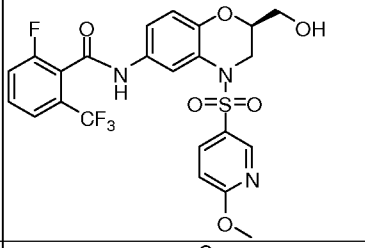
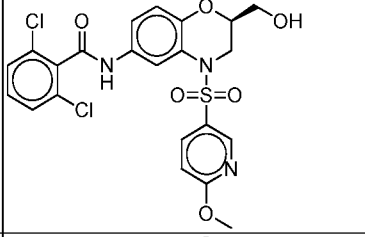
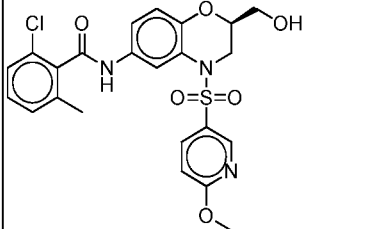
- 191 -

Compound No.	Chemical Structure
VI-10	
VI-11	
VI-12	
VI-13	
VI-14	
VI-15	

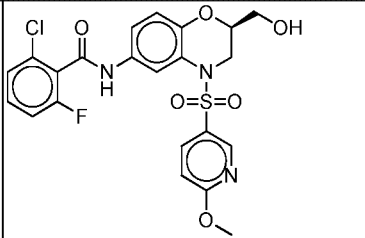
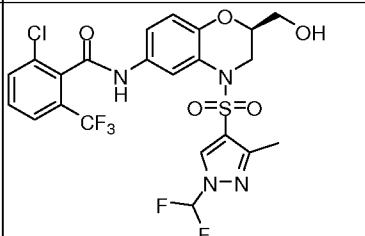
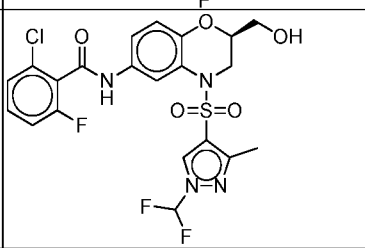
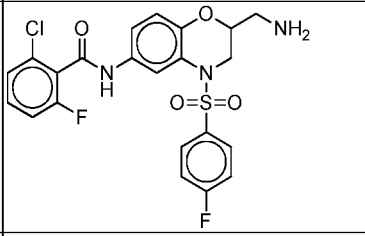
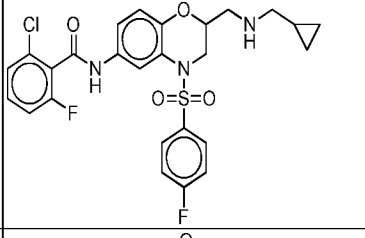
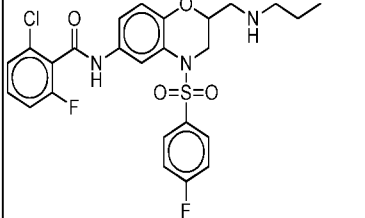
- 192 -

Compound No.	Chemical Structure
VI-16	
VI-17	
VI-18	
VI-19	
VI-20	
VI-21	

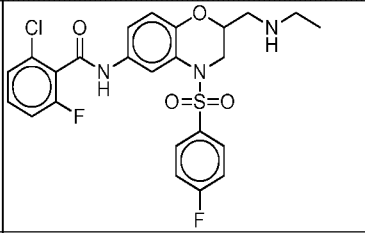
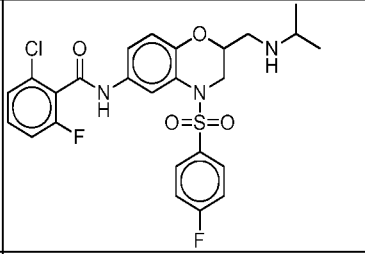
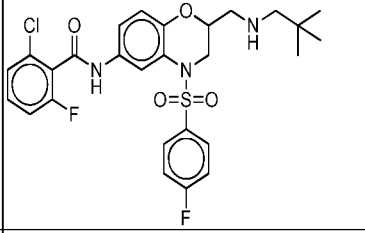
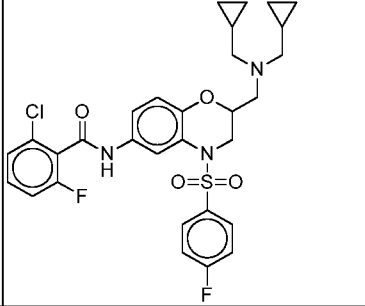
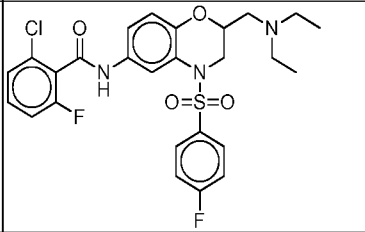
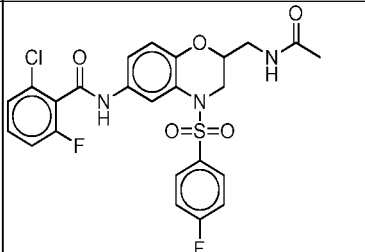
- 193 -

Compound No.	Chemical Structure
VI-22	
VI-23	
VI-24	
VI-25	
VI-26	
VI-27	

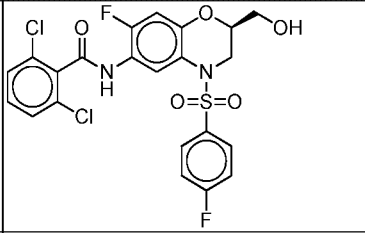
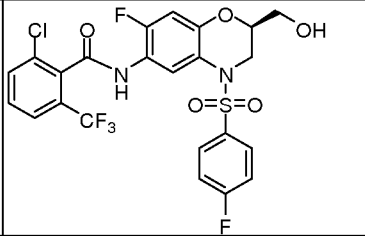
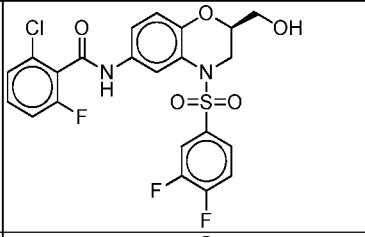
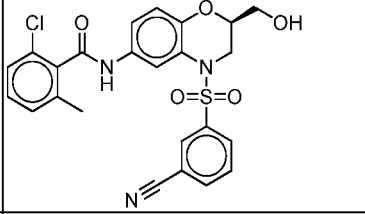
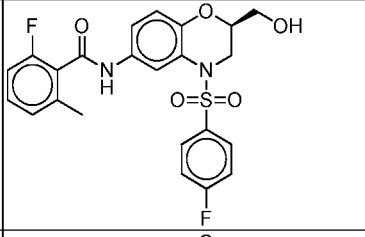
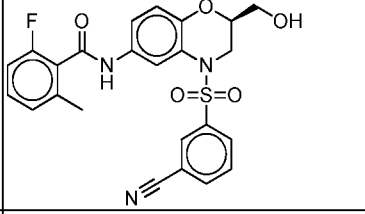
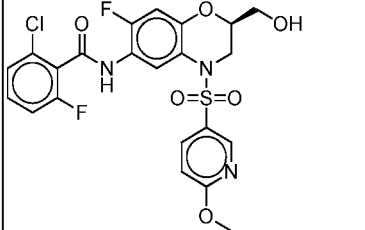
- 194 -

Compound No.	Chemical Structure
VI-28	
VI-29	
VI-30	
VI-31	
VI-32	
VI-33	

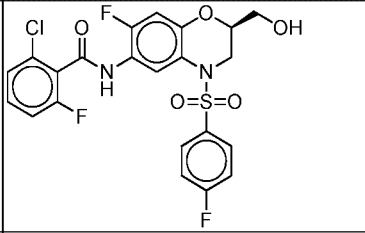
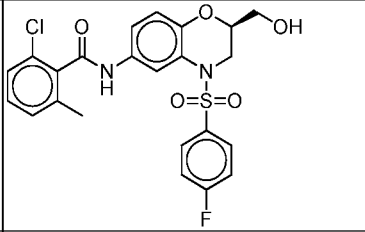
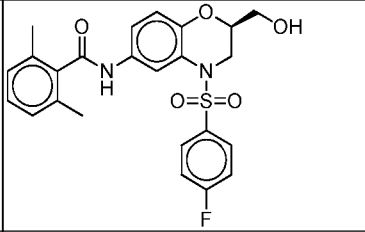
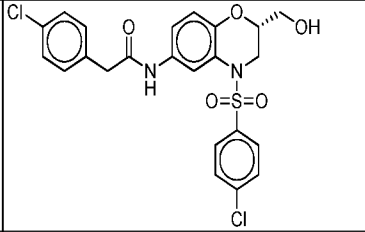
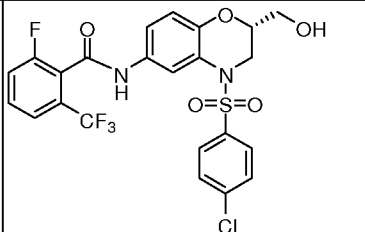
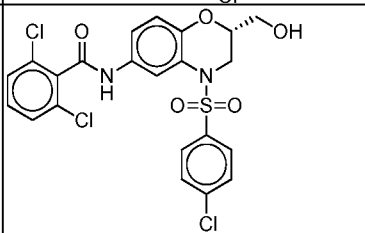
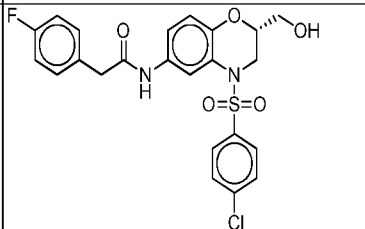
- 195 -

Compound No.	Chemical Structure
VI-34	
VI-35	
VI-36	
VI-37	
VI-38	
VI-39	

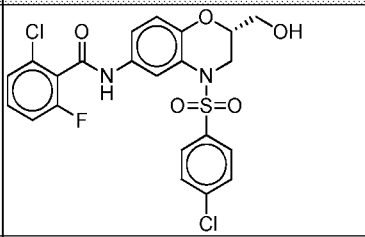
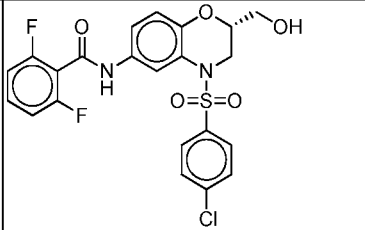
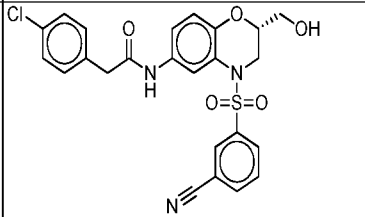
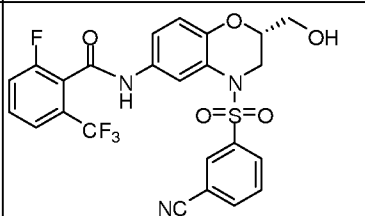
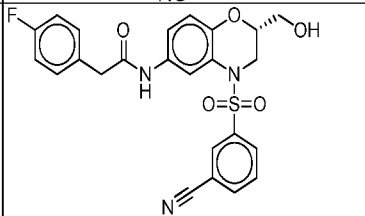
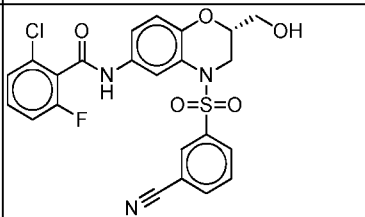
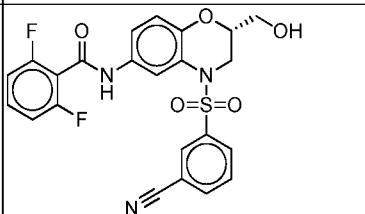
- 196 -

Compound No.	Chemical Structure
VI-40	
VI-41	
VI-42	
VI-43	
VI-44	
VI-45	
VI-46	

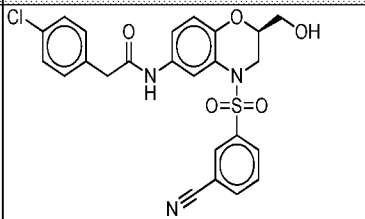
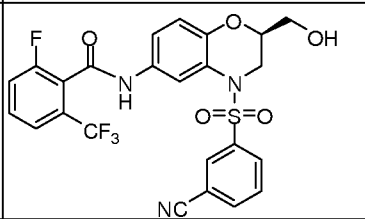
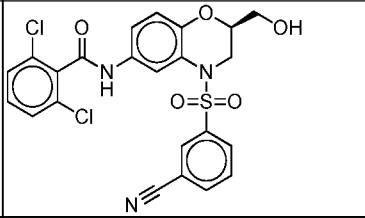
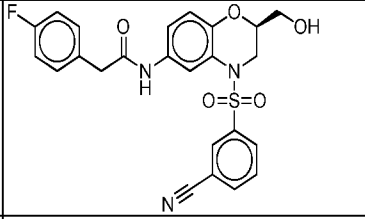
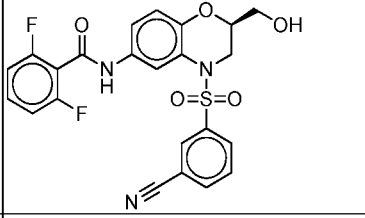
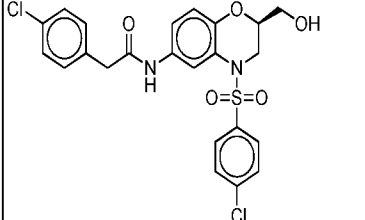
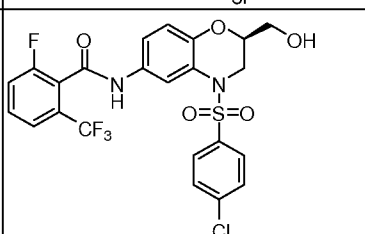
- 197 -

Compound No.	Chemical Structure
VI-47	
VI-48	
VI-49	
VI-50	
VI-51	
VI-52	
VI-53	

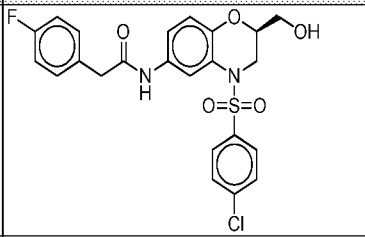
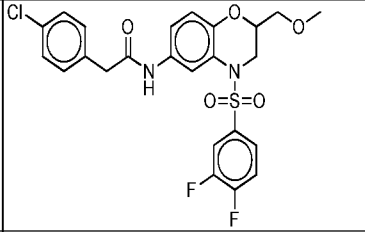
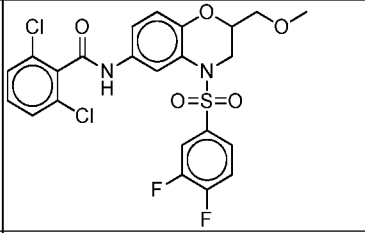
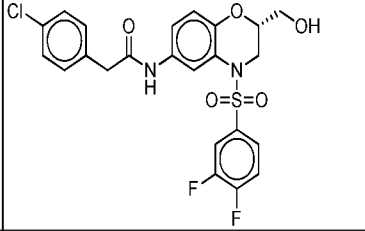
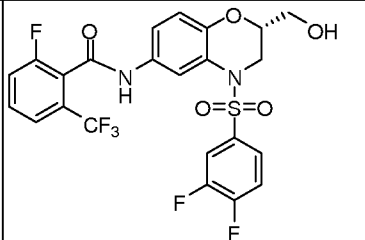
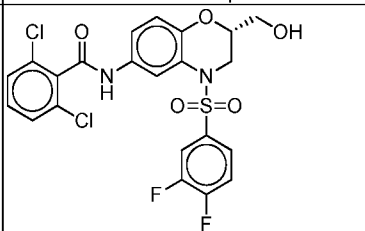
- 198 -

Compound No.	Chemical Structure
VI-54	
VI-55	
VI-56	
VI-57	
VI-58	
VI-59	
VI-60	

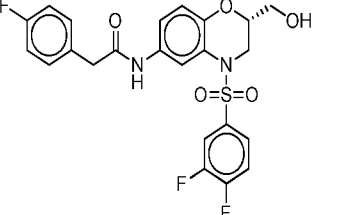
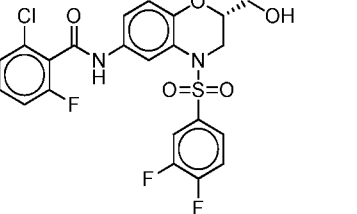
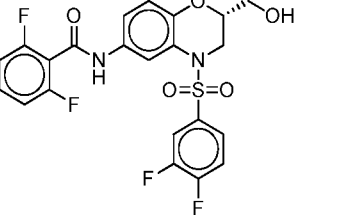
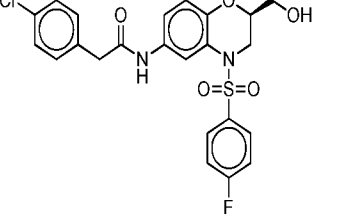
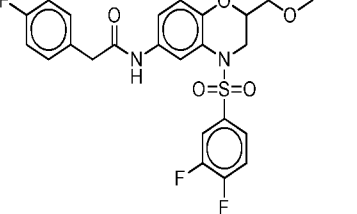
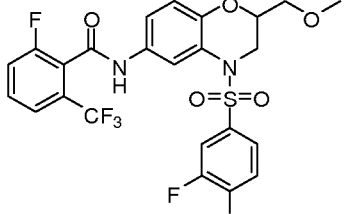
- 199 -

Compound No.	Chemical Structure
VI-61	
VI-62	
VI-63	
VI-64	
VI-65	
VI-66	
VI-67	

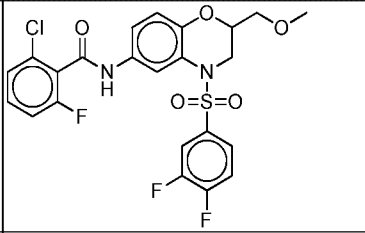
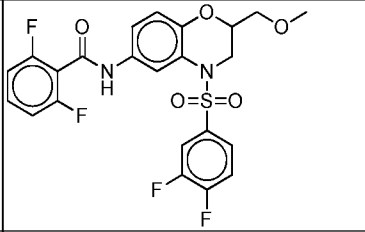
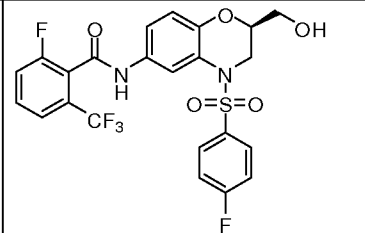
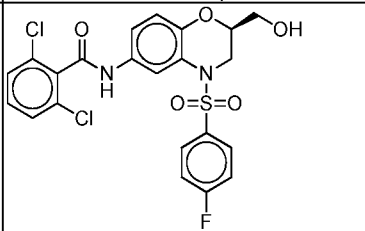
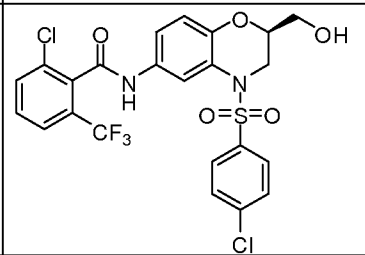
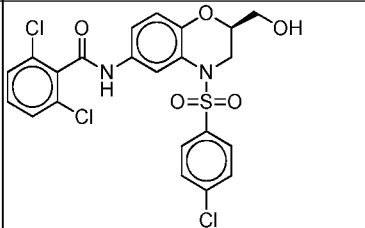
- 200 -

Compound No.	Chemical Structure
VI-68	
VI-69	
VI-70	
VI-71	
VI-72	
VI-73	

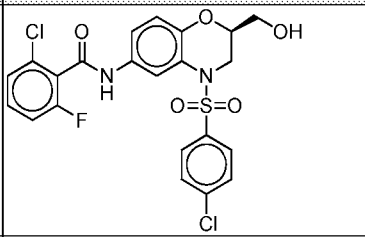
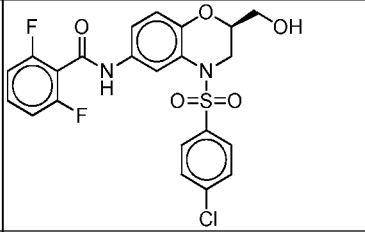
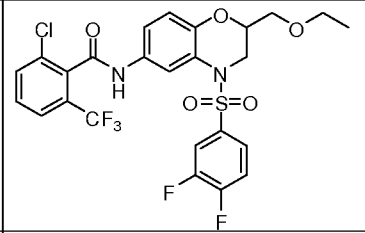
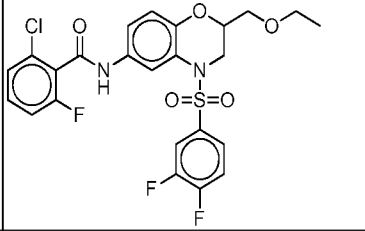
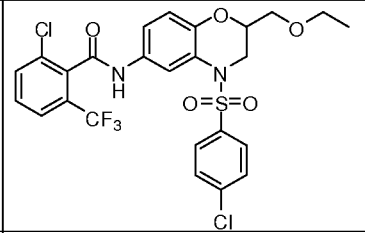
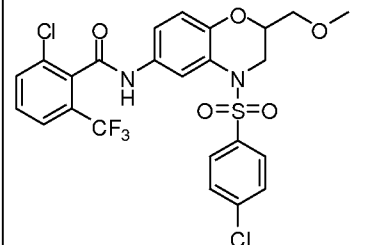
- 201 -

Compound No.	Chemical Structure
VI-74	 <chem>OCC1CN(C1)S(=O)(=O)c2ccc(F)cc2NC(=O)Cc3ccc(F)cc3</chem>
VI-75	 <chem>OCC1CN(C1)S(=O)(=O)c2ccc(F)cc2NC(=O)c3cc(F)c(Cl)cc3</chem>
VI-76	 <chem>OCC1CN(C1)S(=O)(=O)c2ccc(F)cc2NC(=O)c3cc(F)c(F)cc3</chem>
VI-77	 <chem>OCC1CN(C1)S(=O)(=O)c2ccc(F)cc2NC(=O)Cc3ccc(Cl)cc3</chem>
VI-78	 <chem>COCOC1CN(C1)S(=O)(=O)c2ccc(F)cc2NC(=O)Cc3ccc(F)cc3</chem>
VI-79	 <chem>COCOC1CN(C1)S(=O)(=O)c2ccc(F)cc2NC(=O)c3cc(F)c(C(F)(F)F)cc3</chem>

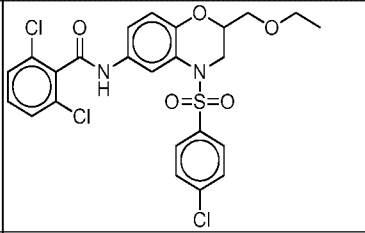
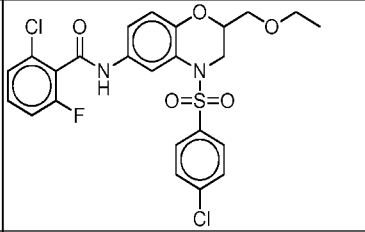
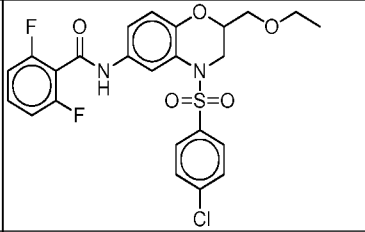
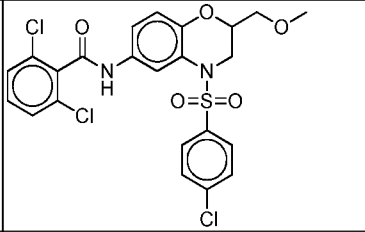
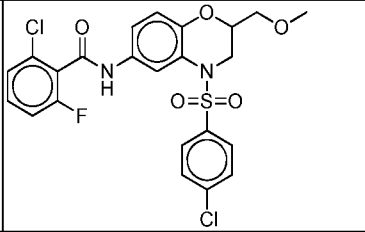
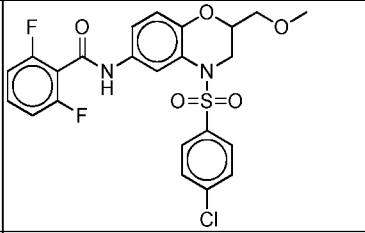
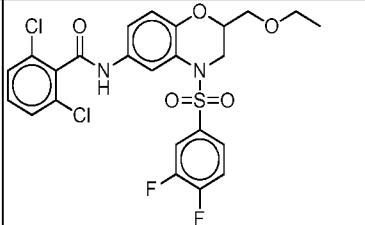
- 202 -

Compound No.	Chemical Structure
VI-80	
VI-81	
VI-82	
VI-83	
VI-84	
VI-85	

- 203 -

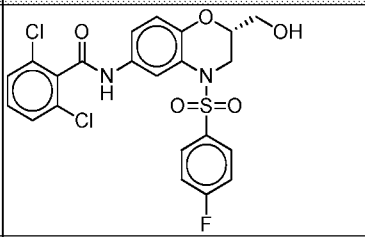
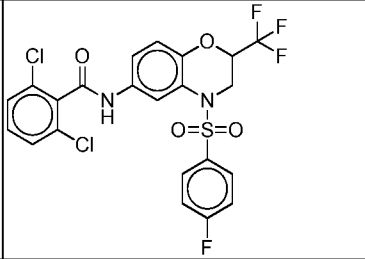
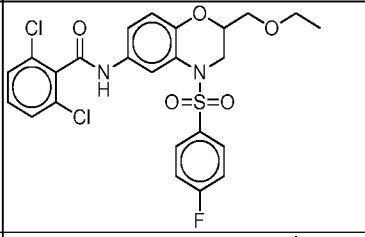
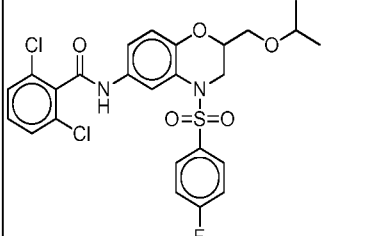
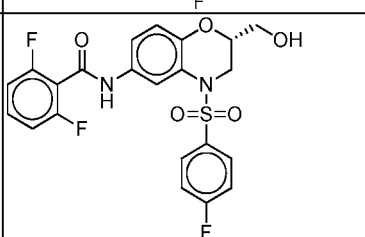
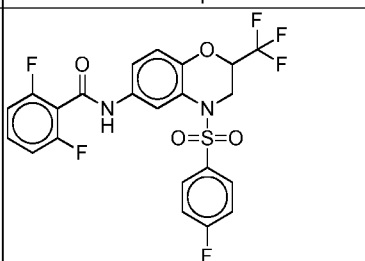
Compound No.	Chemical Structure
VI-86	
VI-87	
VI-88	
VI-89	
VI-90	
VI-91	

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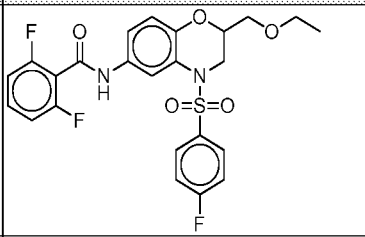
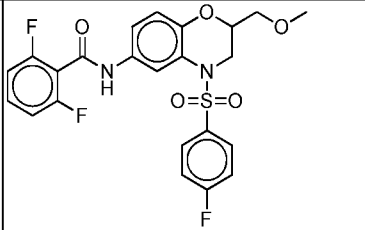
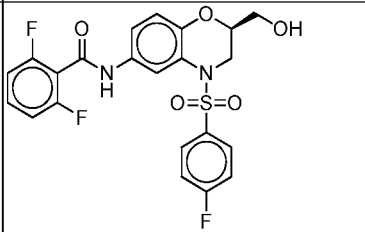
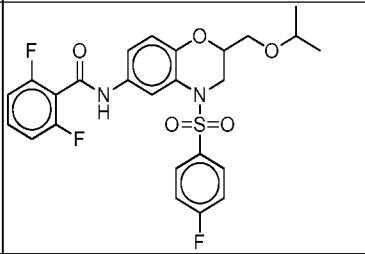
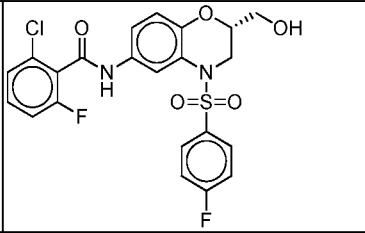
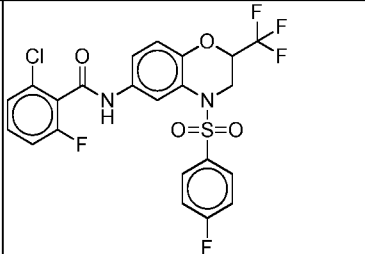
Compound No.	Chemical Structure
VI-92	
VI-93	
VI-94	
VI-95	
VI-96	
VI-97	
VI-98	

Compound No.	Chemical Structure
VI-99	
VI-100	
VI-101	
VI-102	
VI-103	
VI-104	
VI-105	

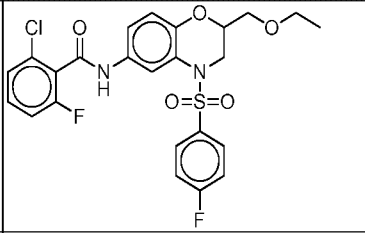
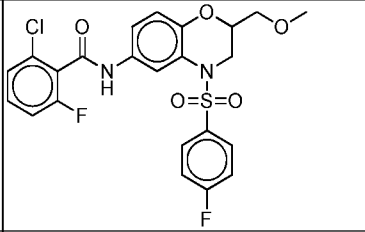
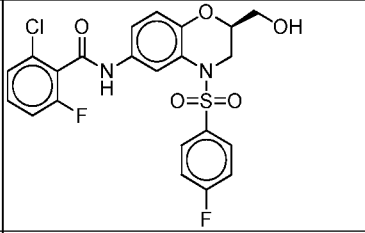
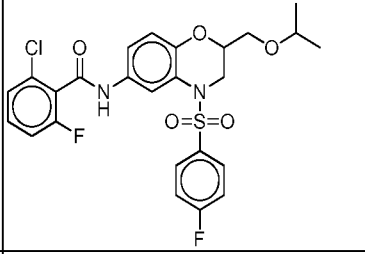
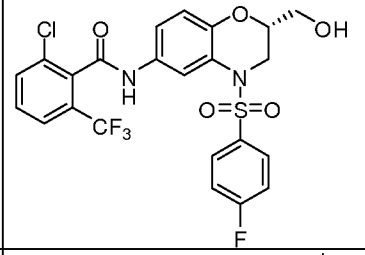
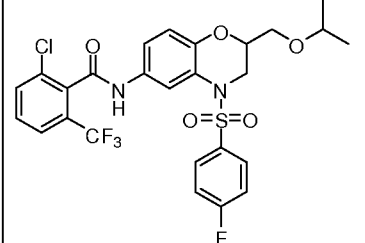
- 206 -

Compound No.	Chemical Structure
VI-106	
VI-107	
VI-108	
VI-109	
VI-110	
VI-111	

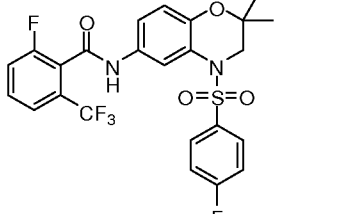
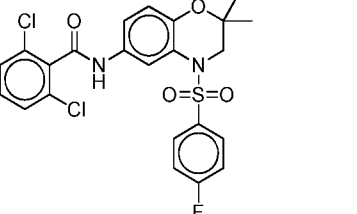
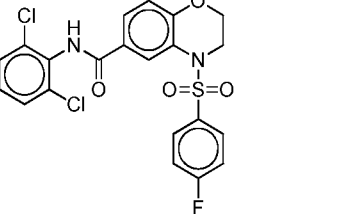
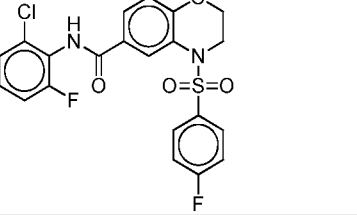
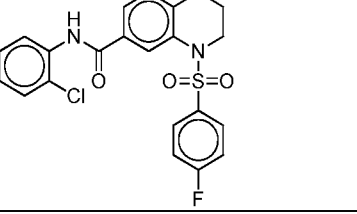
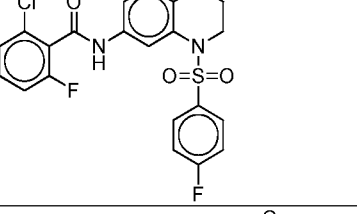
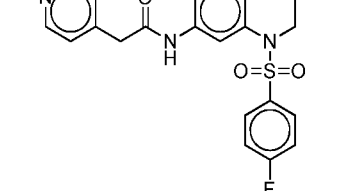
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Compound No.	Chemical Structure
VI-112	
VI-113	
VI-114	
VI-115	
VI-116	
VI-117	

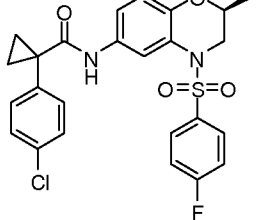
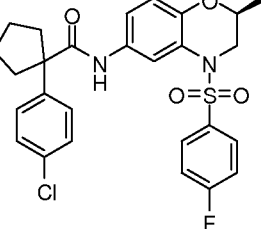
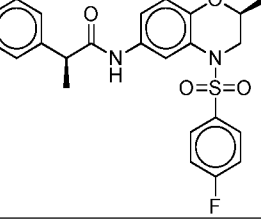
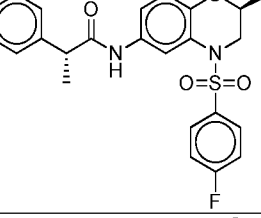
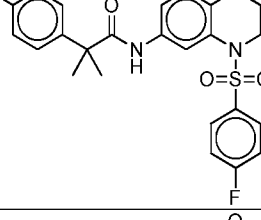
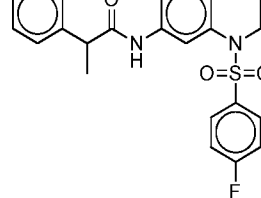
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Compound No.	Chemical Structure
VI-118	
VI-119	
VI-120	
VI-121	
VI-122	
VI-123	

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Compound No.	Chemical Structure
VI-124	
VI-125	
VI-126	
VI-127	
VI-128	
VI-129	
VI-130	

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Compound No.	Chemical Structure
VI-131	
VI-132	
VI-133	
VI-134	
VI-135	
VI-136	

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EXAMPLE 24– Biological Assays for Inhibition of ROR γ

[0311] Exemplary compounds from Examples 1-23 were tested for ability to inhibit ROR γ activity using a ROR γ Reporter Assay and a ROR γ -Ligand Binding Domain TR-FRET Assay. Assay procedures and results are described below.

5 **Part 1 – Procedures for ROR γ Reporter Assay**

General Description

[0312] Inhibition of ROR γ t in cells was determined using a GAL4-UAS reporter system in HEK293 cells employing a luciferase readout. The ROR γ t DNA binding domain (DBD) was replaced with the heterologous yeast GAL4 DBD using standard recombinant DNA methods.

10 The resulting GAL4-ROR γ -LBD fusion construct was placed under the control of a constitutive cytomegalovirus (CMV) promoter by cloning it into the CMV-driven mammalian expression vector pCDNA3.1+- (Promega Corporation, Madison, WI).

[0313] A transcriptional reporter expression construct was used to monitor GAL4-ROR γ activity, which contained five copies of the GAL4 binding site enhancer (UAS) controlling
15 expression of a firefly luciferase reporter. This construct, pGL4.31, is commercially available from Promega Corporation, Madison WI. Both expression constructs were transfected in bulk into HEK-293 cells using standard lipid-based transfection techniques, which allowed the GAL4 ROR γ -LBD fusion protein to drive expression of the luciferase reporter. Control transfections were performed with an empty pCDN3.1+ vector.

20 [0314] The next day, cells were plated into 384 well plates, test compound was added, and the plates were incubated overnight. Test compounds capable of blocking the GAL4-ROR γ fusion protein from initiating expression of the luciferase signal were identified. Promega firefly assays kits were used to stabilize the luciferase signal, and the intensity of the luciferase signal was measured using an EnVision Multilabel Plate Reader (Perkin Elmer, Waltham,
25 MA).

Detailed description of the HEK293 Gal4 Reporter Assay

[0315] HEK 293 cells are transfected with GAL4-NR construct (CMV:NR-LBD in pCDNA3.1neo) and the pGL4.31 GAL4-luciferase reporter construct (Promega). For a background control, use empty pCDNA3.1neo and pGL4.31. Transfection protocol is for a
30 single T75 flask performed with Mirus Trans-It 293 reagent. A 60 μ L aliquot of Trans-IT

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reagent at room temperature is added drop wise to 1.5 mL of Optimem (Invitrogen). The resulting solution is mixed by inversion and incubated for 5-20 minutes at room temperature. This reagent mixture is added to 10 µg of DNA (5 µg of each expression vector used at a concentration of 1 mg/mL). The solution is mixed by inversion and incubated at room
5 temperature for 20 minutes.

[0316] While the Trans-IT reagent and DNA are incubating, harvest HEK-293 cells. Remove media from flasks via aspiration and add enough TrypLE Express (stable Trypsin-like reagent, Invitrogen) to cover the bottom of the flask. The mixture is incubated at room temperature until the cells are visibly loose in the flask (approximately 2-5 minutes). Add an
10 equal volume of complete growth media, and then pipette to achieve a single cell suspension. Spin down 1×10^7 cells and re-suspend the cells in 10 mL of complete growth media (DMEM high glucose/10% dialyzed FBS/ pen/strep; Invitrogen). The cells and transfection mixture are added to one T75 flask. The contents of the T75 flask are mixed and incubated overnight at 37 °C and 5% CO₂.

15 **[0317]** After 16-24 hours, cells are harvested and plated for test compound screening. Cells may be harvested as described above. Next, cells are counted and an appropriate number of cells are spun down. Then, cells are aspirated and re-suspended in complete growth media at a concentration of 0.5×10^6 cells/mL to provide a cell suspension. Plate 20 µL of the cell suspension into a white, tissue-culture treated 384 well plate. (10,000 cells/well).

20 **[0318]** A 10 mM stock solution of test compound in dimethylsulfoxide (DMSO) was diluted to 500x the final test concentration in DMSO, then diluted to 5x the final test concentration with complete growth medium to provide the Test Compound Solution. The concentration of DMSO in the Test Compound Solution was 0.2%. A 5 µL aliquot of Test Compound Solution was added to each test well in the 384 well plate previously plated with the
25 cell suspension. Next, plates are spun briefly and incubated overnight at 37°C and 5% CO₂.

[0319] After 16-24 hours, the luciferase assay is performed. Plates and luciferase reagent (e.g. One-Glo® or Dual Glo®; Promega, Madison, WI) are brought to room temperature. Next, a 25 µL aliquot of luciferase reagent is added to each well. Plates are spun down briefly and incubated at room temperature for 10 minutes. The luciferase signal is measured on an
30 Envision plate reader (Perkin Elmer) set to the ultra sensitive luminescence setting.

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[0320] IC₅₀ values for test compounds were calculated from the luciferase signal data using GraphPad Prism software.

Part II – Procedures for ROR γ -Ligand Binding Domain TR-FRET Assay

[0321] HIS-tagged ROR γ -LBD was recombinantly expressed in SF9 cells using a baculovirus expression system. The protein was not purified. Cells were lysed and the lysate was used as a source for ROR γ -LBD for the assay. A 1:80 dilution of ROR γ -LBD lysate in assay buffer (25 mM HEPES pH 7.0, 100 mM NaCl, 0.01% Tween, 0.1% BSA) was prepared and 5 μ L was added to each well (ROR γ -LBD final concentration ~10 nM). Control wells received lysate from SF9 cells not expressing ROR γ -LBD.

10 [0322] Compounds to be tested were diluted to 100x final test concentration in DMSO and further diluted to 4x final test concentration using assay buffer to provide the test compound mixture. An aliquot (5 μ L) of the test compound mixture was added to each well.

[0323] A 4x stock of biotinylated-LXXLL peptide from SRC1-2 (Biotin-CPSSHSSLTERHKILHRLLEQEGSPS) was prepared in assay buffer and a 5 μ L aliquot added to each well (450 nM final concentration). A 4x solution of europium tagged anti-HIS antibody (2 nM final concentration) and APC conjugated streptavidin (60 nM final concentration) were prepared and a 5 μ L aliquot added to each well.

[0324] The final assay mixture was incubated for 4 hours to overnight, and the fluorescence signal was measured on an Envision plate reader: (Excitation filter = 340 nm; APC emission = 665 nm; Europium emission = 615 nm; dichroic mirror = D400/D630; delay time = 100 μ s, integration time = 200 μ s).

[0325] IC₅₀ values for test compounds were calculated from the quotient of the fluorescence signal at 665 nm divided by the fluorescence signal at 615 nm using GraphPad Prism software.

25 Part III – Results

[0326] ROR γ inhibition data for exemplary compounds is provided in Tables 7-9 below. The term “NA” indicates that no data was available.

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TABLE 7. ROR γ INHIBITION DATA FOR EXEMPLARY TETRAHYDROQUINOLINES

Compound No.	ROR γ FRET IC ₅₀ (μ M)	ROR γ HEK IC ₅₀ (μ M)
4	NA	<15
5	NA	<15
6	NA	<15
III-175	NA	<15
III-176	NA	<15
III-177	NA	<15
III-178	NA	<15
III-179	NA	<15
III-180	NA	<15
III-181	NA	<15
III-182	NA	<15
III-183	NA	<15
III-184	NA	<15
III-185	NA	<15
III-186	NA	<15
III-187	NA	<15
III-188	NA	<15
III-189	NA	<15
III-190	NA	<15
III-191	NA	<15
III-192	NA	<15
III-193	NA	<15
III-194	NA	<15
III-195	NA	<15
III-196	NA	<15
III-197	NA	<15
III-198	NA	15
III-199	NA	<15
III-200	NA	<15
III-201	NA	<15
III-202	NA	<15

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Compound No.	ROR γ FRET IC ₅₀ (μ M)	ROR γ HEK IC ₅₀ (μ M)
III-203	NA	<15
III-204	NA	<15
III-205	NA	<15
III-206	NA	<15
III-207	NA	<15
III-208	NA	<15
III-209	NA	<15
III-210	NA	<15
III-211	NA	<15
III-212	NA	<15
III-213	NA	<15
III-214	NA	<15
III-215	NA	<15
III-216	NA	<15
III-217	NA	<15
III-218	NA	<15
III-219	NA	<15
III-220	NA	>15
III-221	NA	>15
III-222	NA	<15
III-223	NA	<15
III-224	NA	<15
III-225	NA	<15
III-226	NA	<15
III-227	NA	<15
III-228	NA	<15
III-229	NA	<15
III-230	NA	<15
III-231	NA	<15
III-232	NA	>15
III-233	NA	<15
III-234	NA	>15
III-235	NA	>15

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Compound No.	ROR γ FRET IC ₅₀ (μ M)	ROR γ HEK IC ₅₀ (μ M)
III-236	NA	<15
III-237	NA	<15
III-238	NA	<15
III-239	NA	<15
III-240	NA	<15
III-241	NA	<15
III-242	NA	>15
III-243	NA	<15
III-244	NA	<15
III-245	NA	<15
III-246	NA	<15
III-247	NA	<15
III-248	NA	<15
III-249	NA	<15
III-250	NA	<15
III-251	NA	>15
III-252	NA	<15
III-253	NA	<15
III-254	NA	<15
III-255	NA	<15
III-256	NA	<15
III-257	NA	<15
III-258	NA	NA
III-259	NA	<15
III-260	NA	<15
III-261	NA	<15
III-262	NA	<15
III-263	NA	<15
III-264	NA	<15
III-265	NA	<15
III-266	NA	<15
III-267	NA	<15
III-268	NA	<15

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Compound No.	ROR γ FRET IC ₅₀ (μ M)	ROR γ HEK IC ₅₀ (μ M)
III-269	NA	<15
III-270	NA	<15
III-271	NA	<15
III-272	NA	<15
III-273	NA	<15
III-274	NA	<15
III-275	NA	<15
III-276	NA	<15
III-277	NA	>15
III-278	NA	>15
III-279	NA	>15
III-280	NA	>15
III-281	NA	>15
III-282	NA	<15
III-283	NA	<15
III-284	NA	<15
III-285	NA	<15
III-286	NA	<15
III-287	NA	<15
III-288	NA	<15
III-289	NA	<15
III-290	NA	<15
III-291	NA	<15
III-292	NA	<15
III-293	NA	<15
III-294	NA	<15
III-295	NA	<15
III-296	NA	<15
III-297	NA	<15
III-298	NA	<15
III-299	NA	<15
III-300	NA	<15
III-301	NA	<15

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Compound No.	ROR γ FRET IC ₅₀ (μ M)	ROR γ HEK IC ₅₀ (μ M)
III-302	NA	<15
III-303	NA	<15
III-304	NA	<15
III-305	NA	<15
III-306	<15	<15
III-307	<15	<15
III-308	>15	>15
III-309	NA	<15
III-310	NA	<15
III-311	NA	<15
III-312	NA	<15
III-313	<15	<15
III-314	NA	<15
III-315	NA	<15
III-316	NA	<15
III-317	NA	<15
III-318	NA	<15
III-319	NA	<15
III-320	NA	<15
III-321	NA	<15
III-322	NA	<15
III-323	NA	<15
III-324	NA	<15
III-325	NA	<15
III-326	NA	<15
III-327	NA	<15
III-328	NA	<15
III-329	NA	<15
III-330	NA	<15
III-331	NA	<15
III-332	NA	<15
III-333	<15	<15
III-334	NA	<15

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Compound No.	ROR γ FRET IC ₅₀ (μ M)	ROR γ HEK IC ₅₀ (μ M)
III-335	NA	<15
III-336	NA	<15
III-337	NA	<15
III-338	NA	<15
III-339	NA	<15
III-340	NA	<15
III-341	NA	<15
III-342	NA	<15
III-343	NA	<15
III-344	NA	<15
III-345	NA	<15
III-346	NA	<15
III-347	NA	<15
III-348	NA	<15

TABLE 8. ROR γ INHIBITION DATA FOR EXEMPLARY INDAZOLES

Compound No.	ROR γ FRET IC ₅₀ (μ M)	ROR γ HEK IC ₅₀ (μ M)
9	<15	NA
11	<15	NA
10	<15	NA
V-1	<15	NA
V-2	<15	NA
V-3	<15	NA
V-4	<15	NA
V-5	<15	NA
V-6	<15	NA
V-7	<15	NA
V-8	<15	NA
V-9	<15	NA
V-10	<15	NA
V-11	<15	NA
V-12	<15	NA

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Compound No.	ROR γ FRET IC ₅₀ (μ M)	ROR γ HEK IC ₅₀ (μ M)
V-13	<15	NA
V-14	<15	NA
V-15	<15	NA
V-16	<15	NA
V-17	<15	NA
V-18	<15	NA
V-19	<15	NA
V-20	<15	NA
V-21	<15	NA
V-22	<15	NA
V-23	<15	NA
V-24	<15	NA
V-25	<15	NA
V-26	<15	NA
V-27	<15	NA
V-28	<15	NA
V-29	<15	NA
V-30	<15	NA
V-31	<15	NA
V-32	<15	NA
V-33	<15	NA
V-34	<15	NA
V-35	<15	NA
V-36	<15	NA
V-37	<15	NA
V-38	<15	NA
V-39	<15	NA
V-40	<15	NA
V-41	<15	NA
V-42	<15	NA
V-43	<15	NA
V-44	<15	NA
V-45	<15	NA

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Compound No.	ROR γ FRET IC ₅₀ (μ M)	ROR γ HEK IC ₅₀ (μ M)
V-46	<15	NA
V-47	<15	NA
V-48	<15	NA
V-49	<15	NA
V-50	<15	NA
V-51	<15	NA
V-52	<15	NA
V-53	<15	NA
V-54	<15	NA
V-55	<15	NA
V-56	<15	NA
V-57	<15	NA
V-58	<15	NA
V-59	<15	NA
V-60	<15	NA
V-61	<15	NA
V-62	<15	NA
V-63	<15	NA
V-64	<15	NA
V-65	<15	NA
V-66	<15	NA
V-67	<15	NA
V-68	<15	NA
V-69	<15	NA
V-70	<15	NA
V-71	<15	NA
V-72	<15	NA
V-73	<15	NA
V-74	<15	NA
V-75	<15	NA
V-76	<15	NA
V-77	<15	NA
V-78	<15	NA

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Compound No.	ROR γ FRET IC ₅₀ (μ M)	ROR γ HEK IC ₅₀ (μ M)
V-79	<15	NA
V-80	<15	NA
V-81	<15	NA
V-82	<15	NA
V-83	<15	NA
V-84	<15	NA
V-85	<15	NA
V-86	<15	NA
V-87	<15	NA
V-88	<15	NA
V-89	<15	NA
V-90	<15	NA
V-91	<15	NA
V-92	<15	NA
V-93	<15	NA
V-94	<15	NA
V-95	<15	NA
V-96	<15	NA
V-97	<15	NA
V-98	<15	NA
V-99	<15	NA
V-100	<15	NA
V-101	<15	NA
V-102	<15	NA
V-103	<15	NA
V-104	<15	NA
V-105	<15	NA
V-106	<15	NA
V-107	<15	NA
V-108	<15	NA
V-109	<15	NA
V-110	<15	NA
V-111	<15	NA

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Compound No.	ROR γ FRET IC ₅₀ (μ M)	ROR γ HEK IC ₅₀ (μ M)
V-112	<15	NA
V-113	<15	NA
V-114	<15	NA
V-115	<15	NA
V-116	<15	NA
V-117	<15	NA
V-118	<15	NA
V-119	<15	NA
V-120	<15	NA
V-121	<15	NA
V-122	<15	NA
V-123	<15	NA
V-124	<15	NA
V-125	<15	NA
V-126	<15	NA
V-127	<15	NA
V-128	<15	NA
V-129	<15	NA
V-130	<15	NA
V-131	<15	NA
V-132	<15	NA
V-133	<15	NA
V-134	<15	NA
V-135	<15	NA
V-136	<15	NA
V-137	<15	NA
V-138	<15	NA
V-139	<15	NA
V-140	<15	NA
V-141	<15	NA
V-142	<15	NA
V-143	<15	NA
V-144	<15	NA

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Compound No.	ROR γ FRET IC ₅₀ (μ M)	ROR γ HEK IC ₅₀ (μ M)
V-145	<15	NA
V-146	<15	NA
V-147	<15	NA
V-148	<15	NA
V-149	<15	NA
V-150	<15	NA
V-151	<15	NA
V-152	<15	NA
V-153	<15	NA
V-154	<15	NA
V-155	<15	NA
V-156	<15	NA
V-157	<15	NA
V-158	<15	NA
V-159	<15	NA
V-160	<15	NA
V-161	<15	NA
V-162	<15	NA
V-163	<15	NA
V-164	<15	NA
V-165	<15	NA
V-166	<15	NA
V-167	<15	NA
V-168	<15	NA
V-169	<15	NA
V-170	<15	NA
V-171	<15	NA

TABLE 9. ROR γ INHIBITION DATA FOR EXEMPLARY BENZOXAZINES

Compound No.	ROR γ FRET IC ₅₀ (μ M)	ROR γ HEK IC ₅₀ (μ M)
12	<15	<15
13	<15	<15

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Compound No.	ROR γ FRET IC ₅₀ (μ M)	ROR γ HEK IC ₅₀ (μ M)
14	<15	NA
15	<15	<15
16	<15	<15
17	>15	NA
18	>15	NA
19	<15	NA
20	<15	<15
21	<15	<15
22	<15	<15
23	<15	NA
VI-1	<15	<15
VI-2	<15	NA
VI-3	<15	NA
VI-4	<15	NA
VI-5	<15	NA
VI-6	<15	NA
VI-7	<15	NA
VI-8	<15	<15
VI-9	<15	<15
VI-10	<15	<15
VI-11	<15	<15
VI-12	<15	<15
VI-13	<15	<15
VI-14	<15	<15
VI-15	<15	<15
VI-16	<15	NA
VI-17	<15	NA
VI-18	<15	NA
VI-19	<15	NA
VI-20	<15	NA
VI-21	<15	NA
VI-22	<15	NA
VI-23	<15	NA

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Compound No.	ROR γ FRET IC ₅₀ (μ M)	ROR γ HEK IC ₅₀ (μ M)
VI-24	<15	<15
VI-25	<15	<15
VI-26	<15	<15
VI-27	<15	<15
VI-28	<15	<15
VI-29	<15	<15
VI-30	<15	<15
VI-31	<15	NA
VI-32	<15	<15
VI-33	<15	NA
VI-34	<15	NA
VI-35	<15	<15
VI-36	<15	<15
VI-37	<15	<15
VI-38	<15	<15
VI-39	<15	<15
VI-40	<15	<15
VI-41	<15	<15
VI-42	<15	<15
VI-43	<15	<15
VI-44	<15	<15
VI-45	<15	<15
VI-46	<15	<15
VI-47	<15	<15
VI-48	<15	<15
VI-49	<15	<15
VI-50	<15	NA
VI-51	<15	<15
VI-52	<15	<15
VI-53	<15	NA
VI-54	<15	NA
VI-55	<15	NA
VI-56	<15	NA

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Compound No.	ROR γ FRET IC ₅₀ (μ M)	ROR γ HEK IC ₅₀ (μ M)
VI-57	<15	NA
VI-58	<15	NA
VI-59	<15	NA
VI-60	<15	NA
VI-61	<15	NA
VI-62	<15	<15
VI-63	<15	<15
VI-64	<15	NA
VI-65	<15	NA
VI-66	<15	NA
VI-67	<15	<15
VI-68	<15	NA
VI-69	>15	NA
VI-70	<15	<15
VI-71	<15	NA
VI-72	<15	<15
VI-73	<15	<15
VI-74	<15	NA
VI-75	<15	<15
VI-76	<15	<15
VI-77	<15	NA
VI-78	<15	<15
VI-79	<15	<15
VI-80	<15	<15
VI-81	<15	<15
VI-82	<15	<15
VI-83	<15	<15
VI-84	<15	<15
VI-85	<15	<15
VI-86	<15	<15
VI-87	<15	<15
VI-88	<15	<15
VI-89	<15	<15

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Compound No.	ROR γ FRET IC ₅₀ (μ M)	ROR γ HEK IC ₅₀ (μ M)
VI-90	<15	<15
VI-91	<15	<15
VI-92	<15	<15
VI-93	<15	<15
VI-94	<15	<15
VI-95	<15	<15
VI-96	<15	<15
VI-97	<15	<15
VI-98	<15	<15
VI-99	<15	<15
VI-100	<15	<15
VI-101	<15	<15
VI-102	<15	<15
VI-103	<15	<15
VI-104	<15	<15
VI-105	<15	<15
VI-106	<15	<15
VI-107	<15	<15
VI-108	<15	<15
VI-109	<15	<15
VI-110	<15	<15
VI-111	<15	NA
VI-112	<15	<15
VI-113	<15	<15
VI-114	<15	<15
VI-115	<15	<15
VI-116	<15	<15
VI-117	<15	NA
VI-118	<15	<15
VI-119	<15	<15
VI-120	<15	<15
VI-121	<15	<15
VI-122	<15	<15

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Compound No.	ROR γ FRET IC ₅₀ (μ M)	ROR γ HEK IC ₅₀ (μ M)
VI-123	<15	<15
VI-124	<15	<15
VI-125	<15	<15
VI-126	NA	<15
VI-127	NA	<15
VI-128	NA	<15
VI-129	<15	<15
VI-130	<15	NA
VI-131	<15	NA
VI-132	<15	NA
VI-133	<15	NA
VI-134	<15	NA
VI-135	<15	NA
VI-136	<15	NA

INCORPORATION BY REFERENCE

[0327] The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

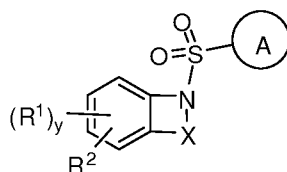
EQUIVALENTS

- 5 [0328] The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the
- 10 claims are intended to be embraced therein.

[0329] What is claimed is:

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1 1. A compound represented by Formula III:



(III)

2
3
4 or a pharmaceutically acceptable salt or solvate thereof; wherein:

5 A is aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl; each of which is
6 optionally substituted with 1, 2, or 3 substituents independently selected from the group
7 consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, -N(R³)(R⁴), -
8 CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-aryl, -
9 O-C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-CO₂R⁶, -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴), -CN,
10 -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), -N(R³)SO₂(C₁₋₆alkyl), heterocyclyl, C(O)R¹¹,
11 -C(R¹¹)(R¹²)OH, -C(O)N(R³)(R⁴), and -N(R³)C(O)N(R³)(R⁴);

12 X is -O-[C(R⁶)₂]_m-ψ, -O-[C(R⁶)(R⁹)C(R⁶)₂]-ψ, -O-[C(R⁶)(R⁹)]-ψ, -O-[C(R⁶)₂-
13 C(hydroxyC₁₋₆alkyl)(R⁶)]-ψ, -C(R⁵)(C₁₋₆alkyl)[C(R⁵)₂]_m-ψ, -[C(R⁵)₂]_m-C(R⁵)(C₁₋₆alkyl)-ψ,
14 -C(R⁵)₂-C(R⁵)(C₁₋₆alkyl)-C(R⁵)₂-ψ, -C(R⁵)₂C(R⁶)=C(R⁶)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ,
15 -C(R⁶)=C(R⁶)-ψ, -N(R⁶)-[C(R⁶)₂]_m-ψ, -N=C(R⁶)-ψ, -N=C(R⁶)C(R⁶)₂-ψ, -N=N-ψ,
16 -C(R⁶)=N-ψ, -C(R¹⁰)=N-ψ, -C(R⁶)₂C(O)C(R⁶)₂-ψ, -[C(R⁶)₂]_m-C(O)-ψ, -C(R⁶)=C(R⁶)C(O)-
17 ψ, -C(O)C(R⁶)=C(R⁶)-ψ, -N(R⁶)-C(O)-ψ, or -C(H)(OR⁶)-[C(R⁶)₂]_m-ψ; wherein ψ is a bond
18 to the sulfonamide ring nitrogen atom in Formula III;

19 R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

20 R² is -N(R⁷)C(O)R⁸, -(C₁₋₂alkylene)-N(R⁷)C(O)R⁸, -N(R⁷)C(O)N(R⁷)(R⁸), or heteroaryl,
21 wherein said heteroaryl group is optionally substituted with 1 or 2 substituents
22 independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆
23 alkyl, C₁₋₆haloalkyl, aryl, heteroaryl, and -N(R³)(R⁴);

24 R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken
25 together with the nitrogen atom to which they are attached form a 3-7 membered
26 heterocyclic ring;

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27 R^5 represents independently for each occurrence hydrogen, halogen, or C_{1-6} alkyl;

28 R^6 and R^7 each represent independently for each occurrence hydrogen or C_{1-6} alkyl;

29 R^8 is aryl, aralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, $-C(R^6)_2$ -cycloalkyl, $-C(R^6)_2$ -
 30 cycloalkenyl, $-C(R^6)_2$ -heterocyclyl, or C_{1-6} alkyl; each of which is optionally substituted
 31 with 1, 2, or 3 substituents independently selected from the group consisting of halogen,
 32 hydroxyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, $-N(R^3)(R^4)$, $-CN$, $-CO_2$ - C_{1-6}
 33 alkyl, $-C(O)$ - C_{1-6} alkyl, $-C(O)N(R^3)(R^4)$, $-S(O)_p$ C_{1-6} alkyl, $-SO_2N(R^3)(R^4)$, and
 34 $-N(R^3)SO_2(C_{1-6}alkyl)$;

35 R^9 and R^{10} each represent independently C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, $-C_{1-6}alkylene$ -
 36 $N(R^3)(R^4)$, $-C_{1-6}alkylene-N(R^3)C(O)$ - $C_{1-6}alkyl$, $-C_{1-6}alkylene-CO_2R^3$, $-C_{1-6}alkylene-CN$, $-C_{1-6}$
 37 $alkylene-C_{1-6}alkoxy$, $-C_{1-6}alkylene-C(O)N(R^3)(R^4)$, $-C(O)N(R^3)(R^4)$, $-C_{1-6}alkylene$ -
 38 $N(R^3)C(O)N(R^3)(R^4)$, $-C_{1-6}alkylene-N(R^3)C(O)$ - $[C(OH)(R^3)(R^4)]$, $-C_{1-6}alkylene-O$ -
 39 $C(O)N(R^3)(R^4)$, $-C_{1-6}alkylene-SO_2N(R^3)(R^4)$, $-C_{1-6}alkylene-N(R^3)SO_2N(R^3)(R^4)$, C_2 -
 40 $alkenyl$, $-arylene-CO_2R^6$, or $-CN$;

41 R^{11} is C_{1-6} alkyl, C_{1-6} haloalkyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl; each of
 42 which is optionally substituted with 1 or 2 substituents independently selected from the
 43 group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, hydroxyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy,
 44 $-CO_2R^3$, and, $-N(R^3)(R^4)$;

45 R^{12} is hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl;
 46 each of which is optionally substituted with 1 or 2 substituents independently selected from
 47 the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, hydroxyl, C_{1-6} alkoxy, C_{1-6}
 48 $haloalkoxy$, $-CO_2R^3$, and, $-N(R^3)(R^4)$;

49 m is 1 or 2;

50 p represents independently for each occurrence 0, 1, or 2;

51 y is 1 or 2; and

52 wherein the stereochemical configuration at a stereocenter in a compound represented
 53 by Formula III is *R*, *S*, or a mixture thereof.

- 1 2. The compound of claim 1, wherein A is phenyl substituted with 1, 2, or 3 substituents
- 2 independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkyl, C_{1-6}
- 3 $haloalkyl$, $-N(R^3)(R^4)$, $-CN$, $-CO_2R^6$, $-C(O)$ - C_{1-6} alkyl, $-C_{1-6}alkylene-N(R^3)(R^4)$, $-C_{1-6}$

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4 C_{1-6} alkylene- C_{1-6} alkoxy, $-\text{C}_{1-6}$ alkylene- CO_2R^6 , $-\text{O}-\text{C}_{1-6}$ alkylene- $\text{N}(\text{R}^3)(\text{R}^4)$, and $-\text{N}(\text{R}^6)\text{C}(\text{O})-\text{C}_{1-6}$
 5 C_{1-6} alkylene- $\text{N}(\text{R}^3)(\text{R}^4)$.

1 3. The compound of claim 1, wherein A is phenyl substituted with 1, 2, or 3 substituents
 2 independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, and
 3 $-\text{CN}$.

1 4. The compound of any one of claims 1-3, wherein X is $-\text{O}-[\text{C}(\text{R}^6)_2]_m-\psi$ or $-\text{O}-$
 2 $[\text{C}(\text{R}^6)(\text{R}^9)\text{C}(\text{R}^6)_2]-\psi$.

1 5. The compound of any one of claims 1-3, wherein X is $-\text{C}(\text{R}^6)=\text{N}-\psi$ or $-\text{C}(\text{R}^{10})=\text{N}-\psi$.

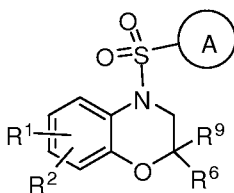
1 6. The compound of any one of claims 1-3, wherein X is $-\text{C}(\text{R}^5)(\text{C}_{1-6}\text{alkyl})[\text{C}(\text{R}^5)_2]_m-\psi$,
 2 $-\text{C}(\text{R}^5)_2-\text{C}(\text{R}^5)(\text{C}_{1-6}\text{alkyl})-\psi$, $-\text{C}(\text{R}^5)_2-\text{C}(\text{R}^5)(\text{C}_{1-6}\text{alkyl})-\text{C}(\text{R}^5)_2-\psi$, $-\text{C}(\text{R}^5)_2\text{C}(\text{R}^6)=\text{C}(\text{R}^6)-\psi$,
 3 $-\text{C}(\text{R}^6)=\text{C}(\text{R}^6)\text{C}(\text{R}^5)_2-\psi$, or $-\text{C}(\text{R}^6)=\text{C}(\text{R}^6)-\psi$.

1 7. The compound of any one of claims 1-6, wherein R^2 is $-\text{N}(\text{R}^7)\text{C}(\text{O})\text{R}^8$.

1 8. The compound of any one of claims 1-7, wherein R^8 is aryl or aralkyl, each of which is
 2 substituted with 1, 2, or 3 substituents independently selected from the group consisting of
 3 halogen, C_{1-6} alkyl, and C_{1-6} haloalkyl.

1 9. The compound of any one of claims 1-7, wherein R^8 is phenyl substituted with 1, 2, or 3
 2 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, and C_{1-6}
 3 haloalkyl.

1 10. The compound of claim 1, wherein said compound is represented by Formula III-C:



(III-C)

4 or a pharmaceutically acceptable salt or solvate thereof; wherein:

5 A is aryl or heteroaryl; each of which is substituted with 1, 2, or 3 substituents
 6 independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkyl, C_{1-6}
 7 haloalkyl, $-\text{CN}$, and $-\text{C}(\text{O})-\text{C}_{1-6}$ alkyl;

8 R^1 represents independently for each occurrence hydrogen, halogen, or C_{1-6} alkyl;

- 233 -

9 R^2 is $-N(R^7)C(O)R^8$;

10 R^3 and R^4 each represent independently hydrogen or C_{1-6} alkyl; or R^3 and R^4 taken
 11 together with the nitrogen atom to which they are attached form a 3-7 membered
 12 heterocyclic ring;

13 R^6 and R^7 each represent independently for each occurrence hydrogen or C_{1-6} alkyl;

14 R^8 is aryl substituted with 1, 2, or 3 substituents independently selected from the group
 15 consisting of halogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

16 R^9 is C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, $-C_{1-6}$ alkylene- $N(R^3)(R^4)$, $-C_{1-6}$ alkylene-
 17 $N(R^3)C(O)-C_{1-6}$ alkyl, $-C_{1-6}$ alkylene-CN, or $-C_{1-6}$ alkylene- C_{1-6} alkoxy; and

18 wherein the stereochemical configuration at a stereocenter in a compound represented
 19 by Formula III-C is *R*, *S*, or a mixture thereof.

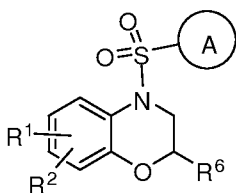
1 11. The compound of claim 10, wherein A is phenyl substituted with 1, 2, or 3 substituents
 2 independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkyl, C_{1-}
 3 $_6$ haloalkyl, and -CN.

1 12. The compound of claim 10 or 11, wherein R^8 is phenyl substituted with 1, 2, or 3
 2 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, and C_{1-}
 3 $_6$ haloalkyl.

1 13. The compound of any one of claims 10-12, wherein R^9 is C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl,
 2 $-C_{1-6}$ alkylene- $N(R^3)C(O)-C_{1-6}$ alkyl, or $-C_{1-6}$ alkylene- C_{1-6} alkoxy.

1 14. The compound of any one of claims 10-13, wherein R^2 is attached to the 6-position of the
 2 benzoxazine ring.

1 15. The compound of claim 1, wherein said compound is represented by Formula III-D:



(III-D)

4 or a pharmaceutically acceptable salt or solvate thereof; wherein:

- 234 -

5 A is aryl or heteroaryl; each of which is substituted with 1, 2, or 3 substituents
 6 independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆
 7 haloalkyl, -CN, and -C(O)-C₁₋₆alkyl;

8 R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

9 R² is -N(R⁷)C(O)R⁸;

10 R⁶ is C₁₋₆alkyl;

11 R⁷ is hydrogen or C₁₋₆alkyl;

12 R⁸ is aryl substituted with 1, 2, or 3 substituents independently selected from the group
 13 consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl; and

14 wherein the stereochemical configuration at a stereocenter in a compound represented
 15 by Formula III-D is *R*, *S*, or a mixture thereof.

1 16. The compound of claim 15, wherein A is phenyl substituted with 1, 2, or 3 substituents
 2 independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆
 3 haloalkyl, and -CN.

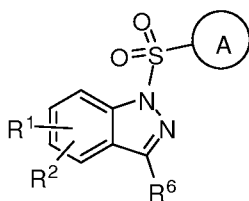
1 17. The compound of claim 15 or 16, wherein R⁸ is phenyl substituted with 1, 2, or 3
 2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆
 3 haloalkyl.

1 18. The compound of any one of claims 15-17, wherein R⁶ is methyl.

1 19. The compound of any one of claims 15-18, wherein R¹ and R⁷ are hydrogen.

1 20. The compound of any one of claims 15-19, wherein R² is attached at the 6-position of the
 2 benzoxazine ring.

1 21. The compound of claim 1, wherein said compound is represented by Formula III-E:



(III-E)

4 or a pharmaceutically acceptable salt or solvate thereof; wherein:

- 235 -

5 A is aryl or heteroaryl; each of which is substituted with 1, 2, or 3 substituents
 6 independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆
 7 haloalkyl, -CN, and -C(O)-C₁₋₆alkyl;

8 R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

9 R² is -N(R⁷)C(O)R⁸;

10 R⁶ is C₁₋₆alkyl;

11 R⁷ is hydrogen or C₁₋₆alkyl;

12 R⁸ is aryl substituted with 1, 2, or 3 substituents independently selected from the group
 13 consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl; and

14 wherein the stereochemical configuration at a stereocenter in a compound represented
 15 by Formula III-E is *R*, *S*, or a mixture thereof.

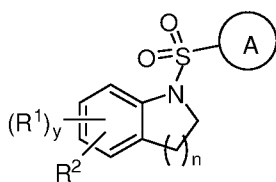
1 22. The compound of claim 21, wherein A is phenyl substituted with 1, 2, or 3 substituents
 2 independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆
 3 haloalkyl, and -CN.

1 23. The compound of claim 21 or 22, wherein R⁸ is phenyl substituted with 1, 2, or 3
 2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆
 3 haloalkyl.

1 24. The compound of any one of claims 21-23, wherein R¹, R⁶, and R⁷ are hydrogen.

1 25. The compound of any one of claims 21-24, wherein R² is attached at the 6-position of the
 2 indazole ring.

1 26. A compound represented by Formula I or II:



(I)

4 or a pharmaceutically acceptable salt or solvate thereof; wherein:

5 A is aryl or aralkyl; each of which is substituted with 1, 2, or 3 substituents
 6 independently selected from the group consisting of C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl,

- 236 -

7 -N(R³)(R⁴), hydroxyl, -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋
8 ₆alkylene-CO₂R⁶, -O-aryl, -O-C₁₋₆alkylene-N(R³)(R⁴), -O-C₁₋₆alkylene-CO₂R⁶,
9 -N(R⁵)C(O)-C₁₋₆alkylene-N(R³)(R⁴), -CN, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), -N(R³)SO₂(C₁₋
10 ₆alkyl), heterocyclyl, -C(O)-C₁₋₆alkyl, -C(O)N(R³)(R⁴), and -N(R³)C(O)N(R³)(R⁴);

11 R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

12 R² is -N(R⁷)C(O)R⁸, -(C₁₋₂alkylene)-N(R⁷)C(O)R⁸, -N(R⁷)C(O)N(R⁷)(R⁸), or heteroaryl,
13 wherein said heteroaryl group is optionally substituted with 1 or 2 substituents
14 independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋
15 ₆alkyl, C₁₋₆haloalkyl, aryl, heteroaryl, and -N(R³)(R⁴);

16 R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken
17 together with the nitrogen atom to which they are attached form a 3-7 membered
18 heterocyclic ring;

19 R⁵ represents independently for each occurrence hydrogen or C₁₋₆alkyl;

20 R⁶ and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;

21 R⁸ is aryl, alkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -C(R⁶)₂-cycloalkyl, -C(R⁶)₂-
22 cycloalkenyl, -C(R⁶)₂-heterocyclyl, or C₁₋₆alkyl; each of which is optionally substituted
23 with 1, 2, or 3 substituents independently selected from the group consisting of halogen,
24 hydroxyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋
25 ₆alkyl, -C(O)-C₁₋₆alkyl, -C(O)N(R³)(R⁴), -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and
26 -N(R³)SO₂(C₁₋₆alkyl);

27 n is 1 or 2;

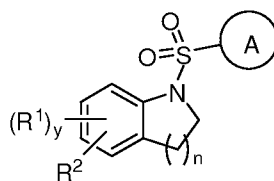
28 p represents independently for each occurrence 0, 1, or 2;

29 y is 1 or 2; and

30 wherein the stereochemical configuration at a stereocenter in a compound represented
31 by Formula I is *R*, *S*, or a mixture thereof;

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32 Formula II is represented by:



33

34

(II)

35

or a pharmaceutically acceptable salt or solvate thereof; wherein:

36

A is cycloalkyl, heterocycloalkyl, or heteroaryl containing at least one ring nitrogen or ring oxygen atom; each of which is optionally substituted with 1, 2, or 3 substituents

37

38

independently selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋

39

6hydroxyalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋

40

6alkylene-CO₂R⁶, -O-aryl, -O-C₁₋₆alkylene-N(R³)(R⁴), -N(R⁵)C(O)-C₁₋₆alkylene-N(R³)(R⁴),

41

-CN, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), -N(R³)SO₂(C₁₋₆alkyl), heterocyclyl, -C(O)-C₁₋₆alkyl,

42

-C(O)N(R³)(R⁴), and -N(R³)C(O)N(R³)(R⁴);

43

R¹ represents independently for each occurrence hydrogen or C₁₋₆alkyl;

44

R² is -N(R⁷)C(O)R⁸, -(C₁₋₂alkylene)-N(R⁷)C(O)R⁸, -N(R⁷)C(O)N(R⁷)(R⁸), or heteroaryl,

45

wherein said heteroaryl group is optionally substituted with 1 or 2 substituents

46

independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋

47

6alkyl, C₁₋₆haloalkyl, aryl, heteroaryl, and -N(R³)(R⁴);

48

R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken

49

together with the nitrogen atom to which they are attached form a 3-7 membered

50

heterocyclic ring;

51

R⁵ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

52

R⁶ and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;

53

R⁸ is aryl, aralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -C(R⁶)₂-cycloalkyl, -C(R⁶)₂-

54

cycloalkenyl, -C(R⁶)₂-heterocyclyl, or C₁₋₆alkyl; each of which is optionally substituted

55

with 1, 2, or 3 substituents independently selected from the group consisting of halogen,

56

hydroxyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋

57

6alkyl, -C(O)-C₁₋₆alkyl, -C(O)N(R³)(R⁴), -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and

58

-N(R³)SO₂(C₁₋₆alkyl);

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59 n is 1 or 2;

60 p represents independently for each occurrence 0, 1, or 2;

61 y is 1 or 2; and

62 wherein the stereochemical configuration at a stereocenter in a compound represented
63 by Formula II is *R*, *S*, or a mixture thereof.

1 27. The compound of claim 26, wherein said compound is a compound of Formula I.

1 28. The compound of claim 27, wherein A is phenyl substituted with 1, 2, or 3 substituents
2 independently selected from the group consisting of C₁₋₆haloalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆-
3 alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆-
4 alkylene-N(R³)(R⁴), and -N(R⁵)C(O)-C₁₋₆alkylene-N(R³)(R⁴).

1 29. The compound of claim 26, wherein said compound is a compound of Formula II.

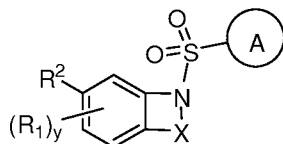
1 30. The compound of any one of claims 26-29, wherein n is 2, and R² is attached at the 7-
2 position of the tetrahydroquinoline ring.

1 31. The compound of claim any one of claims 26-30, wherein A is phenyl substituted with 1, 2,
2 or 3 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆-
3 alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆-
4 alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R⁶)C(O)-C₁₋₆-
5 alkylene-N(R³)(R⁴).

1 32. The compound of any one of claims 26-31, wherein R² is -N(R⁷)C(O)R⁸.

1 33. The compound of any one of claims 26-32, wherein R⁸ is aryl substituted with 1, 2, or 3
2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆-
3 haloalkyl.

1 34. A compound represented by Formula IV:



(IV)

4 or a pharmaceutically acceptable salt or solvate thereof; wherein:

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5 A is aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl; each of which is
 6 optionally substituted with 1, 2, or 3 substituents independently selected from the group
 7 consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, -N(R³)(R⁴), -
 8 CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C<sub>1-
 9 6</sub>alkylene-N(R³)(R⁴), -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴), -CN, -S(O)_pC₁₋₆alkyl,
 10 -SO₂N(R³)(R⁴), -N(R³)SO₂(C₁₋₆alkyl), heterocyclyl, -C(O)R¹¹, -C(R¹¹)(R¹²)OH,
 11 -C(O)N(R³)(R⁴), and -N(R³)C(O)N(R³)(R⁴);

12 X is -C(R⁵)₂C(R⁶)=C(R⁶)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, -C(O)-[C(R⁶)₂]_m-ψ,
 13 -C(R⁶)₂C(O)C(R⁶)₂-ψ, -[C(R⁶)₂]_m-C(O)-ψ, -C(R⁶)=C(R⁶)C(O)-ψ, -C(O)C(R⁶)=C(R⁶)-ψ,
 14 -O-[C(R⁶)₂]_m-ψ, -O-[C(R⁶)(R⁹)C(R⁶)₂]-ψ, -O-[C(R⁶)(R⁹)]-ψ, -O-[C(R⁶)₂-C(hydroxyC<sub>1-
 15 6</sub>alkyl)(R⁶)]-ψ, -C(R⁶)=N-ψ, -C(R¹⁰)=N-ψ, or -C(H)(OR⁶)-[C(R⁶)₂]_m-ψ; wherein ψ is a
 16 bond to the sulfonamide ring nitrogen atom in Formula IV;

17 R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

18 R² is -C(O)N(R⁷)(R⁸) or -N(R⁷)C(O)N(R⁷)(R⁸);

19 R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken
 20 together with the nitrogen atom to which they are attached form a 3-7 membered
 21 heterocyclic ring;

22 R⁵ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

23 R⁶ and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;

24 R⁸ is aryl, aralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -C(R⁶)₂-cycloalkyl, -C(R⁶)₂-
 25 cycloalkenyl, -C(R⁶)₂-heterocyclyl, or C₁₋₆alkyl; each of which is optionally substituted
 26 with 1, 2, or 3 substituents independently selected from the group consisting of halogen,
 27 hydroxyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C<sub>1-
 28 6</sub>alkyl, -C(O)-C₁₋₆alkyl, -C(O)N(R³)(R⁴), -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and
 29 -N(R³)SO₂(C₁₋₆alkyl);

30 R⁹ and R¹⁰ each represent independently C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, -C₁₋₆alkylene-
 31 N(R³)(R⁴), -C₁₋₆alkylene-N(R³)C(O)-C₁₋₆alkyl, -C₁₋₆alkylene-CO₂R³, -C₁₋₆alkylene-CN, -C<sub>1-
 32 6</sub>alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-C(O)N(R³)(R⁴), -C(O)N(R³)(R⁴), -C₁₋₆alkylene-
 33 N(R³)C(O)N(R³)(R⁴), -C₁₋₆alkylene-N(R³)C(O)-[C(OH)(R³)(R⁴)], -C₁₋₆alkylene-O-

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34 C(O)N(R³)(R⁴), -C₁₋₆alkylene-SO₂N(R³)(R⁴), -C₁₋₆alkylene-N(R³)SO₂N(R³)(R⁴), C₂₋
 35 ₄alkenyl, -arylene-CO₂R⁶, or -CN;

36 R¹¹ is C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl; each of
 37 which is optionally substituted with 1 or 2 substituents independently selected from the
 38 group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, hydroxyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy,
 39 -CO₂R³, and, -N(R³)(R⁴);

40 R¹² is hydrogen, C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl;
 41 each of which is optionally substituted with 1 or 2 substituents independently selected from
 42 the group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, hydroxyl, C₁₋₆alkoxy, C₁₋
 43 ₆haloalkoxy, -CO₂R³, and, -N(R³)(R⁴);

44 m is 1 or 2;

45 p represents independently for each occurrence 0, 1, or 2;

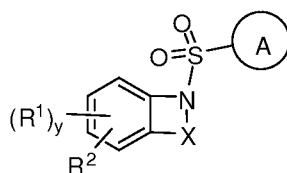
46 y is 1 or 2; and

47 wherein the stereochemical configuration at a stereocenter in a compound represented
 48 by Formula IV is *R*, *S*, or a mixture thereof.

1 35. The compound of claim 34, wherein A is phenyl substituted with 1, 2, or 3 substituents
 2 independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋
 3 ₆haloalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋
 4 ₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴).

1 36. The compound of claim 34 or 35, wherein R⁸ is aryl substituted with 1, 2, or 3 substituents
 2 independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆haloalkyl.

1 37. A pharmaceutical composition comprising (i) a pharmaceutically acceptable carrier and (ii)
 2 a compound represented by Formula V or VI:



(V)

5 or a pharmaceutically acceptable salt or solvate thereof; wherein:

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6 A is aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl; each of which is
 7 optionally substituted with 1, 2, or 3 substituents independently selected from the group
 8 consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋
 9 ₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-aryl, -O-C₁₋
 10 ₆alkylene-N(R³)(R⁴), -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴), -CN, -S(O)_pC₁₋₆alkyl,
 11 -SO₂N(R³)(R⁴), -N(R³)SO₂(C₁₋₆alkyl), heterocyclyl, -C(O)R¹¹, -C(R¹¹)(R¹²)OH,
 12 -C(O)N(R³)(R⁴), and -N(R³)C(O)N(R³)(R⁴);

13 X is -[C(R⁵)₂]_n-ψ, -C(R⁵)₂C(R⁶)=C(R⁶)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, -C(R⁶)=C(R⁶)-ψ, -O-
 14 [C(R⁶)₂]_m-ψ, -O-[C(R⁶)(R⁹)C(R⁶)₂]-ψ, -O-[C(R⁶)(R⁹)]-ψ, -O-[C(R⁶)₂-C(hydroxyC₁₋
 15 ₆alkyl)(R⁶)]-ψ, -N(R⁶)-[C(R⁶)₂]_m-ψ, -N=C(R⁶)-ψ, -N=C(R⁶)C(R⁶)₂-ψ, -N=N-ψ, -C(R⁶)=N-
 16 ψ, -C(R¹⁰)=N-ψ, -C(R⁶)₂C(O)C(R⁶)₂-ψ, -[C(R⁶)₂]-C(O)-ψ, -C(R⁶)=C(R⁶)C(O)-ψ,
 17 -C(O)C(R⁶)=C(R⁶)-ψ, -N(R⁶)-C(O)-ψ, or -C(H)(OR⁶)-[C(R⁶)₂]_m-ψ; wherein ψ is a bond to
 18 the sulfonamide ring nitrogen atom in Formula V;

19 R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

20 R² is -N(R⁷)C(O)R⁸, -(C₁₋₂alkylene)-N(R⁷)C(O)R⁸, -N(R⁷)C(O)N(R⁷)(R⁸), or heteroaryl,
 21 wherein said heteroaryl group is optionally substituted with 1 or 2 substituents
 22 independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋
 23 ₆alkyl, C₁₋₆haloalkyl, aryl, heteroaryl, and -N(R³)(R⁴);

24 R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken
 25 together with the nitrogen atom to which they are attached form a 3-7 membered
 26 heterocyclic ring;

27 R⁵ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

28 R⁶ and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;

29 R⁸ is aryl, aralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -C(R⁶)₂-cycloalkyl, -C(R⁶)₂-
 30 cycloalkenyl, -C(R⁶)₂-heterocyclyl, or C₁₋₆alkyl; each of which is optionally substituted
 31 with 1, 2, or 3 substituents independently selected from the group consisting of halogen,
 32 hydroxyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋
 33 ₆alkyl, -C(O)-C₁₋₆alkyl, -C(O)N(R³)(R⁴), -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and
 34 -N(R³)SO₂(C₁₋₆alkyl);

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35 R⁹ and R¹⁰ each represent independently C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, -C₁₋₆alkylene-
 36 N(R³)(R⁴), -C₁₋₆alkylene-N(R³)C(O)-C₁₋₆alkyl, -C₁₋₆alkylene-CO₂R³, -C₁₋₆alkylene-CN, -C₁₋₆-
 37 alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-C(O)N(R³)(R⁴), -C(O)N(R³)(R⁴), -C₁₋₆alkylene-
 38 N(R³)C(O)N(R³)(R⁴), -C₁₋₆alkylene-N(R³)C(O)-[C(OH)(R³)(R⁴)], -C₁₋₆alkylene-O-
 39 C(O)N(R³)(R⁴), -C₁₋₆alkylene-SO₂N(R³)(R⁴), -C₁₋₆alkylene-N(R³)SO₂N(R³)(R⁴), C₂-
 40 alkenyl, -arylene-CO₂R⁶, or -CN;

41 R¹¹ is C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl; each of
 42 which is optionally substituted with 1 or 2 substituents independently selected from the
 43 group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, hydroxyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy,
 44 -CO₂R³, and, -N(R³)(R⁴);

45 R¹² is hydrogen, C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl;
 46 each of which is optionally substituted with 1 or 2 substituents independently selected from
 47 the group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, hydroxyl, C₁₋₆alkoxy, C₁₋₆-
 48 haloalkoxy, -CO₂R³, and, -N(R³)(R⁴);

49 n is 1, 2, or 3;

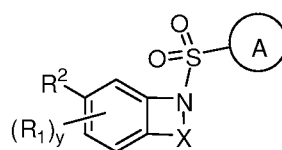
50 m is 1 or 2;

51 p represents independently for each occurrence 0, 1, or 2;

52 y is 1 or 2; and

53 wherein the stereochemical configuration at a stereocenter in a compound represented
 54 by Formula V is *R*, *S*, or a mixture thereof; and

55 Formula VI is represented by:



(VI)

56 or a pharmaceutically acceptable salt or solvate thereof; wherein:

59 A is aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl; each of which is
 60 optionally substituted with 1, 2, or 3 substituents independently selected from the group
 61 consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, -N(R³)(R⁴), -

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62 CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-aryl, -
 63 O-C₁₋₆alkylene-N(R³)(R⁴), -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴), -CN, -S(O)_pC₁₋₆alkyl,
 64 -SO₂N(R³)(R⁴), -N(R³)SO₂(C₁₋₆alkyl), heterocyclyl, -C(O)R¹¹, -C(R¹¹)(R¹²)OH,
 65 -C(O)N(R³)(R⁴), and -N(R³)C(O)N(R³)(R⁴);

66 X is -[C(R⁵)₂]₃-ψ, -C(R⁵)₂C(R⁶)=C(R⁶)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, -C(R⁶)=C(R⁶)-ψ,
 67 -C(O)-[C(R⁶)₂]_m-ψ, -C(R⁶)₂C(O)C(R⁶)₂-ψ, -[C(R⁶)₂]_m-C(O)-ψ, -C(R⁶)=C(R⁶)C(O)-ψ,
 68 -C(O)C(R⁶)=C(R⁶)-ψ, -C(R⁶)=N-ψ, -C(R¹⁰)=N-ψ, -O-[C(R⁶)₂]_m-ψ, -O-[C(R⁶)(R⁹)C(R⁶)₂]-
 69 ψ, -O-[C(R⁶)(R⁹)]-ψ, -O-[C(R⁶)₂-C(hydroxyC₁₋₆alkyl)(R⁶)]-ψ, or -C(H)(OR⁶)-[C(R⁶)₂]_m-ψ;
 70 wherein ψ is a bond to the sulfonamide ring nitrogen atom in Formula VI;

71 R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

72 R² is -C(O)N(R⁷)(R⁸);

73 R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken
 74 together with the nitrogen atom to which they are attached form a 3-7 membered
 75 heterocyclic ring;

76 R⁵ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

77 R⁶ and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;

78 R⁸ is aryl or aralkyl; each of which is optionally substituted with 1, 2, or 3 substituents
 79 independently selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, and
 80 -CN;

81 R⁹ and R¹⁰ each represent independently C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, -C₁₋₆alkylene-
 82 N(R³)(R⁴), -C₁₋₆alkylene-N(R³)C(O)-C₁₋₆alkyl, -C₁₋₆alkylene-CO₂R³, -C₁₋₆alkylene-CN, -C₁₋₆-
 83 6alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-C(O)N(R³)(R⁴), -C(O)N(R³)(R⁴), -C₁₋₆alkylene-
 84 N(R³)C(O)N(R³)(R⁴), -C₁₋₆alkylene-N(R³)C(O)-[C(OH)(R³)(R⁴)], -C₁₋₆alkylene-O-
 85 C(O)N(R³)(R⁴), -C₁₋₆alkylene-SO₂N(R³)(R⁴), -C₁₋₆alkylene-N(R³)SO₂N(R³)(R⁴), C₂-
 86 4alkenyl, -arylene-CO₂R⁶, or -CN;

87 R¹¹ is C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl; each of
 88 which is optionally substituted with 1 or 2 substituents independently selected from the
 89 group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, hydroxyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy,
 90 -CO₂R³, and, -N(R³)(R⁴);

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91 R^{12} is hydrogen, C₁₋₆alkyl, C₁₋₆haloalkyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl;
92 each of which is optionally substituted with 1 or 2 substituents independently selected from
93 the group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, hydroxyl, C₁₋₆alkoxy, C₁₋₆
94 haloalkoxy, -CO₂R³, and, -N(R³)(R⁴);

95 m is 1 or 2;

96 p is 0, 1, or 2;

97 y is 1 or 2; and

98 wherein the stereochemical configuration at a stereocenter in a compound represented
99 by Formula VI is *R*, *S*, or a mixture thereof.

1 38. The pharmaceutical composition of claim 37, wherein said compound is a compound of
2 Formula V.

1 39. The pharmaceutical composition of claim 38, wherein A is aryl substituted with 1, 2, or 3
2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, C₁₋₆
3 haloalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆
4 alkylene-N(R³)(R⁴), and -N(R⁶)C(O)-C₁₋₆alkylene-N(R³)(R⁴).

1 40. The pharmaceutical composition of claim 38, wherein A is phenyl substituted with 1, 2, or 3
2 substituents independently selected from the group consisting of halogen, hydroxyl, C₁₋₆
3 alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂R⁶, -C(O)-C₁₋₆alkyl, -C₁₋₆alkylene-N(R³)(R⁴), -
4 C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R⁶)C(O)-
5 C₁₋₆alkylene-N(R³)(R⁴).

1 41. The pharmaceutical composition of claim 38, wherein A is phenyl substituted with 1, 2, or 3
2 substituents independently selected from the group consisting of halogen and C₁₋₆haloalkyl.

1 42. The pharmaceutical composition of claim 38, wherein A is phenyl substituted at the 4-
2 position with fluorine or chlorine.

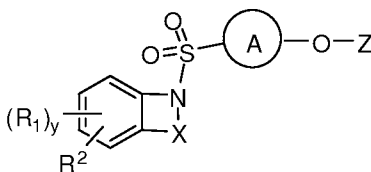
1 43. The pharmaceutical composition of any one of claims 38-42, wherein X is -(CH₂)₃-ψ.

1 44. The pharmaceutical composition of claim 43, wherein R² is attached to the 7-position of the
2 tetrahydroquinoline ring.

1 45. The pharmaceutical composition of any one of claims 38-42, wherein X is -O-[C(R⁶)₂]_m-ψ
2 or -O-[C(R⁶)(R⁹)C(R⁶)₂]-ψ.

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- 1 46. The pharmaceutical composition of any one of claims 38-42, wherein X is $-C(R^6)=N-\psi$ or
2 $-C(R^{10})=N-\psi$.
- 1 47. The pharmaceutical composition of any one of claims 38-46, wherein R^2 is $-N(R^7)C(O)R^8$.
- 1 48. The pharmaceutical composition of any one of claims 38-47, wherein R^8 is aryl or aralkyl;
2 each of which is optionally substituted with 1, 2, or 3 substituents independently selected
3 from the group consisting of halogen, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl,
4 $-N(R^3)(R^4)$, $-CN$, $-CO_2-C_{1-6}$ alkyl, $-C(O)-C_{1-6}$ alkyl, and $-S-C_{1-6}$ alkyl.
- 1 49. The pharmaceutical composition of any one of claims 38-47, R^8 is aryl substituted with 1, 2,
2 or 3 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, and
3 C_{1-6} haloalkyl.
- 1 50. The pharmaceutical composition of any one of claims 38-47, R^8 is phenyl substituted with 1,
2 2, or 3 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl,
3 and C_{1-6} haloalkyl.
- 1 51. The pharmaceutical composition of claim 37, wherein said compound is a compound of
2 Formula VI.
- 1 52. The pharmaceutical composition of claim 51, wherein A is aryl substituted with 1, 2, or 3
2 substituents independently selected from the group consisting of halogen, hydroxyl, C_{1-}
3 6 alkyl, C_{1-6} haloalkyl, $-N(R^3)(R^4)$, $-CO_2R^6$, $-C_{1-6}$ alkylene- $N(R^3)(R^4)$, $-C_{1-6}$ alkylene- CO_2R^6 ,
4 $-O-C_{1-6}$ alkylene- $N(R^3)(R^4)$, and $-N(R^6)C(O)-C_{1-6}$ alkylene- $N(R^3)(R^4)$.
- 1 53. The pharmaceutical composition of claim 51, wherein A is phenyl substituted at the 4-
2 position with fluorine or chlorine.
- 1 54. The pharmaceutical composition of any one of claims 51-53, wherein R^8 is phenyl
2 substituted with 2 or 3 substituents independently selected from the group consisting of
3 halogen, C_{1-6} alkyl, and C_{1-6} haloalkyl.
- 1 55. A compound of Formula VII:



(VII)

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4 or a pharmaceutically acceptable salt or solvate thereof; wherein:

5 A is arylene, aralkylene, heteroarylene, cycloalkylene, or heterocycloalkylene; each of
6 which is optionally substituted with 1, 2, or 3 substituents independently selected from the
7 group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl,
8 -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆
9 alkylene-CO₂R⁶, -O-aryl, -O-C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-CO₂R⁶, -N(R⁶)C(O)-
10 C₁₋₆alkylene-N(R³)(R⁴), -CN, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), -N(R³)SO₂(C₁₋₆alkyl),
11 heterocyclyl, -C(O)R¹¹, -C(R¹¹)(R¹²)OH, -C(O)N(R³)(R⁴), and -N(R³)C(O)N(R³)(R⁴);

12 X is -C(R⁵)(C₁₋₆alkyl)[C(R⁵)₂]_m-ψ, -[C(R⁵)₂]_m-C(R⁵)(C₁₋₆alkyl)-ψ, -C(R⁵)₂-C(R⁵)(C₁₋₆
13 alkyl)-C(R⁵)₂-ψ, -C(R⁵)₂C(R⁶)=C(R⁶)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, -C(R⁶)=C(R⁶)-ψ, -O-
14 [C(R⁶)₂]_m-ψ, -O-[C(R⁶)(R⁹)C(R⁶)₂]-ψ, -O-[C(R⁶)(R⁹)]-ψ, -O-[C(R⁶)₂-C(hydroxyC₁₋₆
15 alkyl)(R⁶)]-ψ, -N(R⁶)-[C(R⁶)₂]_m-ψ, -N=C(R⁶)-ψ, -N=C(R⁶)C(R⁶)₂-ψ, -N=N-ψ, -C(R⁶)=N-
16 ψ, -C(R¹⁰)=N-ψ, -C(O)-[C(R⁶)₂]_m-ψ, -C(R⁶)₂C(O)C(R⁶)₂-ψ, -[C(R⁶)₂]_m-C(O)-ψ,
17 -C(R⁶)=C(R⁶)C(O)-ψ, -C(O)C(R⁶)=C(R⁶)-ψ, -N(R⁶)-C(O)-ψ, or -C(H)(OR⁶)-[C(R⁶)₂]_m-ψ;
18 wherein ψ is a bond to the sulfonamide ring nitrogen atom in Formula VII;

19 Z is C₁₋₆alkyl or C₁₋₆haloalkyl;

20 R¹ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

21 R² is -N(R⁷)C(O)R⁸, -(C₁₋₂alkylene)-N(R⁷)C(O)R⁸, -N(R⁷)C(O)N(R⁷)(R⁸), or heteroaryl,
22 wherein said heteroaryl group is optionally substituted with 1 or 2 substituents
23 independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆
24 alkyl, C₁₋₆haloalkyl, aryl, heteroaryl, and -N(R³)(R⁴);

25 R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken
26 together with the nitrogen atom to which they are attached form a 3-7 membered
27 heterocyclic ring;

28 R⁵ represents independently for each occurrence hydrogen, halogen, or C₁₋₆alkyl;

29 R⁶ and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;

30 R⁸ is aryl, aralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -C(R⁶)₂-cycloalkyl, -C(R⁶)₂-
31 cycloalkenyl, -C(R⁶)₂-heterocyclyl, or C₁₋₆alkyl; each of which is optionally substituted
32 with 1, 2, or 3 substituents independently selected from the group consisting of halogen,
33 hydroxyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋

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34 C_6 alkyl, $-\text{C}(\text{O})-\text{C}_{1-6}$ alkyl, $-\text{C}(\text{O})\text{N}(\text{R}^3)(\text{R}^4)$, $-\text{S}(\text{O})_p\text{C}_{1-6}$ alkyl, $-\text{SO}_2\text{N}(\text{R}^3)(\text{R}^4)$, and
 35 $-\text{N}(\text{R}^3)\text{SO}_2(\text{C}_{1-6}\text{alkyl})$;

36 R^9 and R^{10} each represent independently C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, $-\text{C}_{1-6}$ alkylene-
 37 $\text{N}(\text{R}^3)(\text{R}^4)$, $-\text{C}_{1-6}$ alkylene- $\text{N}(\text{R}^3)\text{C}(\text{O})-\text{C}_{1-6}$ alkyl, $-\text{C}_{1-6}$ alkylene- CO_2R^3 , $-\text{C}_{1-6}$ alkylene-CN, $-\text{C}_{1-}$
 38 C_6 alkylene- C_{1-6} alkoxy, $-\text{C}_{1-6}$ alkylene- $\text{C}(\text{O})\text{N}(\text{R}^3)(\text{R}^4)$, $-\text{C}(\text{O})\text{N}(\text{R}^3)(\text{R}^4)$, $-\text{C}_{1-6}$ alkylene-
 39 $\text{N}(\text{R}^3)\text{C}(\text{O})\text{N}(\text{R}^3)(\text{R}^4)$, $-\text{C}_{1-6}$ alkylene- $\text{N}(\text{R}^3)\text{C}(\text{O})-[\text{C}(\text{OH})(\text{R}^3)(\text{R}^4)]$, $-\text{C}_{1-6}$ alkylene-O-
 40 $\text{C}(\text{O})\text{N}(\text{R}^3)(\text{R}^4)$, $-\text{C}_{1-6}$ alkylene- $\text{SO}_2\text{N}(\text{R}^3)(\text{R}^4)$, $-\text{C}_{1-6}$ alkylene- $\text{N}(\text{R}^3)\text{SO}_2\text{N}(\text{R}^3)(\text{R}^4)$, C_{2-}
 41 C_4 alkenyl, $-\text{arylene}-\text{CO}_2\text{R}^6$, or $-\text{CN}$;

42 R^{11} is C_{1-6} alkyl, C_{1-6} haloalkyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl; each of
 43 which is optionally substituted with 1 or 2 substituents independently selected from the
 44 group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, hydroxyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy,
 45 $-\text{CO}_2\text{R}^3$, and, $-\text{N}(\text{R}^3)(\text{R}^4)$;

46 R^{12} is hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl;
 47 each of which is optionally substituted with 1 or 2 substituents independently selected from
 48 the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, hydroxyl, C_{1-6} alkoxy, C_{1-}
 49 C_6 haloalkoxy, $-\text{CO}_2\text{R}^3$, and, $-\text{N}(\text{R}^3)(\text{R}^4)$;

50 m is 1 or 2;

51 p represents independently for each occurrence 0, 1, or 2;

52 y is 1 or 2; and

53 wherein the stereochemical configuration at a stereocenter in a compound represented
 54 by Formula VII is *R*, *S*, or a mixture thereof.

1 56. The compound of claim 55, wherein A is aryl substituted with 1, 2, or 3 substituents
 2 independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkyl, C_{1-}
 3 C_6 haloalkyl, $-\text{N}(\text{R}^3)(\text{R}^4)$, $-\text{CN}$, $-\text{CO}_2\text{R}^6$, $-\text{C}(\text{O})-\text{C}_{1-6}$ alkyl, $-\text{C}_{1-6}$ alkylene- $\text{N}(\text{R}^3)(\text{R}^4)$, $-\text{C}_{1-}$
 4 C_6 alkylene- C_{1-6} alkoxy, $-\text{C}_{1-6}$ alkylene- CO_2R^6 , $-\text{O}-\text{C}_{1-6}$ alkylene- $\text{N}(\text{R}^3)(\text{R}^4)$, and $-\text{N}(\text{R}^6)\text{C}(\text{O})-\text{C}_{1-}$
 5 C_6 alkylene- $\text{N}(\text{R}^3)(\text{R}^4)$.

1 57. The compound of claim 55, wherein A is phenyl substituted with 1, 2, or 3 substituents
 2 independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkyl, C_{1-}
 3 C_6 haloalkyl, $-\text{N}(\text{R}^3)(\text{R}^4)$, $-\text{CN}$, $-\text{CO}_2\text{R}^6$, $-\text{C}(\text{O})-\text{C}_{1-6}$ alkyl, $-\text{C}_{1-6}$ alkylene- $\text{N}(\text{R}^3)(\text{R}^4)$, $-\text{C}_{1-}$

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4 $\text{C}_6\text{alkylene-C}_{1-6}\text{alkoxy}$, $-\text{C}_{1-6}\text{alkylene-CO}_2\text{R}^6$, $-\text{O-C}_{1-6}\text{alkylene-N(R}^3\text{)(R}^4\text{)}$, and $-\text{N(R}^6\text{)C(O)-C}_{1-}$
 5 $\text{C}_6\text{alkylene-N(R}^3\text{)(R}^4\text{)}$.

1 58. The compound of any one of claims 55-57, wherein X is $-\text{O-[C(R}^6\text{)}_2]_m-\psi$ or $-\text{O-}$
 2 $[\text{C(R}^6\text{)(R}^9\text{)C(R}^6\text{)}_2]-\psi$.

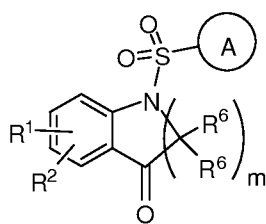
1 59. The compound of any one of claims 55-57, wherein X is $-\text{C(R}^6\text{)=N-}\psi$ or $-\text{C(R}^{10}\text{)=N-}\psi$.

1 60. The compound of any one of claims 55-59, wherein R^2 is $-\text{N(R}^7\text{)C(O)R}^8$.

1 61. The compound of any one of claims 55-60, wherein R^8 is aryl substituted with 1, 2, or 3
 2 substituents independently selected from the group consisting of halogen, $\text{C}_{1-6}\text{alkyl}$, and C_{1-}
 3 $\text{C}_6\text{haloalkyl}$.

1 62. The compound of any one of claims 55-60, wherein R^8 is phenyl substituted with 1, 2, or 3
 2 substituents independently selected from the group consisting of halogen, $\text{C}_{1-6}\text{alkyl}$, and C_{1-}
 3 $\text{C}_6\text{haloalkyl}$.

1 63. A compound of Formula VIII:



(VIII)

4 or a pharmaceutically acceptable salt or solvate thereof; wherein:

5 A is aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl; each of which is
 6 optionally substituted with 1, 2, or 3 substituents independently selected from the group
 7 consisting of halogen, hydroxyl, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{haloalkyl}$, $-\text{N(R}^3\text{)(R}^4\text{)}$, $-\text{CO}_2\text{R}^6$, $-\text{C}_{1-}$
 8 $\text{C}_6\text{alkylene-N(R}^3\text{)(R}^4\text{)}$, $-\text{C}_{1-6}\text{alkylene-C}_{1-6}\text{alkoxy}$, $-\text{C}_{1-6}\text{alkylene-CO}_2\text{R}^6$, $-\text{O-C}_{1-}$
 9 $\text{C}_6\text{alkylene-N(R}^3\text{)(R}^4\text{)}$, $-\text{C}_{1-6}\text{alkylene-CO}_2\text{R}^6$, $-\text{N(R}^5\text{)C(O)-C}_{1-6}\text{alkylene-N(R}^3\text{)(R}^4\text{)}$, $-\text{CN}$, $-$
 10 $\text{S(O)}_p\text{C}_{1-6}\text{alkyl}$, $-\text{SO}_2\text{N(R}^3\text{)(R}^4\text{)}$, and $-\text{N(R}^3\text{)SO}_2(\text{C}_{1-6}\text{alkyl})$;

11 R^1 represents independently for each occurrence hydrogen, halogen, or $\text{C}_{1-6}\text{alkyl}$;

12 R^2 is $-\text{N(R}^7\text{)C(O)R}^8$, $-(\text{C}_{1-2}\text{alkylene)-N(R}^7\text{)C(O)R}^8$, or heteroaryl, wherein said
 13 heteroaryl group is optionally substituted with 1 or 2 substituents independently selected

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14 from the group consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, aryl,
15 heteroaryl, and -N(R³)(R⁴);

16 R³ and R⁴ each represent independently hydrogen or C₁₋₆alkyl; or R³ and R⁴ taken
17 together with the nitrogen atom to which they are attached form a 3-7 membered
18 heterocyclic ring;

19 R⁵, R⁶, and R⁷ each represent independently for each occurrence hydrogen or C₁₋₆alkyl;

20 R⁸ is aryl, aralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, -C(R⁶)₂-cycloalkyl, -C(R⁶)₂-
21 cycloalkenyl, -C(R⁶)₂-heterocyclyl, or C₁₋₆alkyl; each of which is optionally substituted
22 with 1, 2, or 3 substituents independently selected from the group consisting of halogen,
23 hydroxyl, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂-C₁₋₆alkyl, -C(O)-C₁₋₆
24 alkyl, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), and -N(R³)SO₂(C₁₋₆alkyl);

25 m is 1 or 2;

26 p represents independently for each occurrence 0, 1, or 2; and

27 wherein the stereochemical configuration at a stereocenter in a compound represented
28 by Formula VIII is *R*, *S*, or a mixture thereof.

1 64. The compound of claim 63, wherein A is aryl substituted with 1, 2, or 3 substituents
2 independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆
3 haloalkyl, -N(R³)(R⁴), -CN, -CO₂R⁶, -C(O)-C₁₋₆alkyl, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆
4 alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R⁵)C(O)-C₁₋₆
5 alkylene-N(R³)(R⁴).

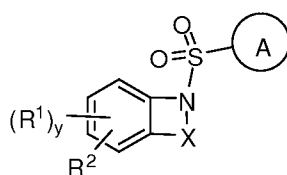
1 65. The compound of claim 63 or 64, wherein A is phenyl substituted with 1, 2, or 3 substituents
2 independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆
3 haloalkyl, -N(R³)(R⁴), -CN, -CO₂R⁶, -C(O)-C₁₋₆alkyl, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆
4 alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R⁵)C(O)-C₁₋₆
5 alkylene-N(R³)(R⁴).

1 66. The compound of any one of claims 63-65, wherein R² is -N(R⁷)C(O)R⁸.

1 67. The compound of any one of claims 63-66, wherein R⁸ is aryl substituted with 1, 2, or 3
2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆
3 haloalkyl.

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- 1 68. The compound of any one of claims 63-66, wherein R⁸ is phenyl substituted with 1, 2, or 3
 2 substituents independently selected from the group consisting of halogen, C₁₋₆alkyl, and C₁₋₆
 3 haloalkyl.
- 1 69. A compound in any one of Tables I-VI described herein or a pharmaceutically acceptable
 2 salt thereof.
- 1 70. The compound of claim 69, wherein the compound is any one of compounds VI-25 to VI-69
 2 or VI-115 to VI-123 described herein.
- 1 71. A pharmaceutical composition comprising a (i) a pharmaceutically acceptable carrier and
 2 (ii) a compound of claim 55, 63, or 69.
- 1 72. A method of treating a disorder selected from the group consisting of an immune disorder
 2 and inflammatory disorder, comprising administering a therapeutically effective amount of
 3 a compound of Formula IX to a subject in need thereof to ameliorate a symptom of the
 4 disorder, wherein Formula IX is represented by:



(IX)

7 or a pharmaceutically acceptable salt or solvate thereof; wherein:

8 A is aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl; each of which is
 9 optionally substituted with 1, 2, or 3 substituents independently selected from the group
 10 consisting of halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆
 11 hydroxyalkyl, -N(R³)(R⁴), -CO₂R⁶, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋₆alkylene-C₁₋₆alkoxy, -C₁₋₆
 12 alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), -O-C₁₋₆alkylene-CO₂R⁶, -N(R⁶)C(O)-C₁₋₆
 13 alkylene-N(R³)(R⁴), -O-aryl, -CN, -S(O)_pC₁₋₆alkyl, -SO₂N(R³)(R⁴), -N(R³)SO₂(C₁₋₆alkyl),
 14 heterocyclyl, -C(O)R¹¹, -C(R¹¹)(R¹²)OH, -C(O)N(R³)(R⁴), and -N(R³)C(O)N(R³)(R⁴);

15 X is -[C(R⁵)₂]_n-ψ, -C(R⁵)₂C(R⁶)=C(R⁶)-ψ, -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, -C(R⁶)=C(R⁶)-ψ, -O-
 16 [C(R⁶)₂]_m-ψ, -O-[C(R⁶)(R⁹)C(R⁶)₂]-ψ, -O-[C(R⁶)(R⁹)]-ψ, -O-[C(R⁶)₂-C(hydroxyC₁₋₆
 17 alkyl)(R⁶)]-ψ, -N(R⁶)-[C(R⁶)₂]_m-ψ, -N=C(R⁶)-ψ, -N=C(R⁶)C(R⁶)₂-ψ, -N=N-ψ, -C(R⁶)=N-
 18 ψ, -C(R¹⁰)=N-ψ, -C(O)-[C(R⁶)₂]_m-ψ, -C(R⁶)₂C(O)C(R⁶)₂-ψ, -[C(R⁶)₂]_m-C(O)-ψ,

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19 $-C(R^6)=C(R^6)C(O)-\psi$, $-C(O)C(R^6)=C(R^6)-\psi$, $-N(R^6)-C(O)-\psi$, or $-C(H)(OR^6)-[C(R^6)_2]_m-\psi$;
 20 wherein ψ is a bond to the sulfonamide ring nitrogen atom in Formula IX;

21 R^1 represents independently for each occurrence hydrogen, halogen, or C_{1-6} alkyl;

22 R^2 is $-N(R^7)C(O)R^8$, $-(C_{1-2}alkylene)-N(R^7)C(O)R^8$, $-C(O)N(R^7)(R^8)$,
 23 $-N(R^7)C(O)N(R^7)(R^8)$, or heteroaryl, wherein said heteroaryl group is optionally substituted
 24 with 1 or 2 substituents independently selected from the group consisting of halogen,
 25 hydroxyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, aryl, heteroaryl, and $-N(R^3)(R^4)$;

26 R^3 and R^4 each represent independently hydrogen or C_{1-6} alkyl; or R^3 and R^4 taken
 27 together with the nitrogen atom to which they are attached form a 3-7 membered
 28 heterocyclic ring;

29 R^5 represents independently for each occurrence hydrogen, halogen, or C_{1-6} alkyl;

30 R^6 and R^7 each represent independently for each occurrence hydrogen or C_{1-6} alkyl;

31 R^8 is aryl, aralkyl, cycloalkyl, cycloalkenyl, heterocyclyl, $-C(R^6)_2$ -cycloalkyl, $-C(R^6)_2$ -
 32 cycloalkenyl, $-C(R^6)_2$ -heterocyclyl, or C_{1-6} alkyl; each of which is optionally substituted
 33 with 1, 2, or 3 substituents independently selected from the group consisting of halogen,
 34 hydroxyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, $-N(R^3)(R^4)$, $-CN$, $-CO_2$ - C_{1-}
 35 6 alkyl, $-C(O)-C_{1-6}$ alkyl, $-C(O)N(R^3)(R^4)$, $-S(O)_pC_{1-6}$ alkyl, $-SO_2N(R^3)(R^4)$, and
 36 $-N(R^3)SO_2(C_{1-6}alkyl)$;

37 R^9 and R^{10} each represent independently C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, $-C_{1-6}alkylene-$
 38 $N(R^3)(R^4)$, $-C_{1-6}alkylene-N(R^3)C(O)-C_{1-6}alkyl$, $-C_{1-6}alkylene-CO_2R^3$, $-C_{1-6}alkylene-CN$, $-C_{1-}$
 39 6 alkylene- C_{1-6} alkoxy, $-C_{1-6}alkylene-C(O)N(R^3)(R^4)$, $-C(O)N(R^3)(R^4)$, $-C_{1-6}alkylene-$
 40 $N(R^3)C(O)N(R^3)(R^4)$, $-C_{1-6}alkylene-N(R^3)C(O)-[C(OH)(R^3)(R^4)]$, $-C_{1-6}alkylene-O-$
 41 $C(O)N(R^3)(R^4)$, $-C_{1-6}alkylene-SO_2N(R^3)(R^4)$, $-C_{1-6}alkylene-N(R^3)SO_2N(R^3)(R^4)$, C_{2-}
 42 4 alkenyl, $-arylene-CO_2R^6$, or $-CN$;

43 R^{11} is C_{1-6} alkyl, C_{1-6} haloalkyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl; each of
 44 which is optionally substituted with 1 or 2 substituents independently selected from the
 45 group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, hydroxyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy,
 46 $-CO_2R^3$, and, $-N(R^3)(R^4)$;

47 R^{12} is hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, aryl, aralkyl, heteroaryl, or heterocycloalkyl;
 48 each of which is optionally substituted with 1 or 2 substituents independently selected from

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49 the group consisting of halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, hydroxyl, C₁₋₆alkoxy, C₁₋
 50 ₆haloalkoxy, -CO₂R³, and, -N(R³)(R⁴);

51 n is 1, 2, or 3;

52 m is 1 or 2;

53 p represents independently for each occurrence 0, 1, or 2;

54 y is 1 or 2; and

55 wherein the stereochemical configuration at a stereocenter in a compound represented
 56 by Formula IX is *R*, *S*, or a mixture thereof.

1 73. The method of claim 72, wherein A is aryl substituted with 1, 2, or 3 substituents
 2 independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋
 3 ₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂R⁶, -C(O)-C₁₋₆alkyl, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋
 4 ₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R⁶)C(O)-C₁₋
 5 ₆alkylene-N(R³)(R⁴).

1 74. The method of claim 72, wherein A is phenyl substituted with 1, 2, or 3 substituents
 2 independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋
 3 ₆haloalkyl, -N(R³)(R⁴), -CN, -CO₂R⁶, -C(O)-C₁₋₆alkyl, -C₁₋₆alkylene-N(R³)(R⁴), -C₁₋
 4 ₆alkylene-C₁₋₆alkoxy, -C₁₋₆alkylene-CO₂R⁶, -O-C₁₋₆alkylene-N(R³)(R⁴), and -N(R⁶)C(O)-C₁₋
 5 ₆alkylene-N(R³)(R⁴).

1 75. The method of claim 72, wherein A is phenyl substituted with 1, 2, or 3 substituents
 2 independently selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋
 3 ₆haloalkyl, and -CN.

1 76. The method of claim 72, wherein A is phenyl substituted with 1, 2, or 3 substituents
 2 independently selected from the group consisting of halogen and C₁₋₆haloalkyl.

1 77. The method of any one of claims 72-76, wherein X is -O-[C(R⁶)₂]_m-ψ or -O-
 2 [C(R⁶)(R⁹)C(R⁶)₂]-ψ.

1 78. The method of any one of claims 72-76, wherein X is -C(R⁶)=N-ψ or -C(R¹⁰)=N-ψ.

1 79. The method of any one of claims 72-76, wherein X is -C(R⁵)(C₁₋₆alkyl)[C(R⁵)₂]_m-ψ,
 2 -[C(R⁵)₂]_m-C(R⁵)(C₁₋₆alkyl)-ψ, -C(R⁵)₂-C(R⁵)(C₁₋₆alkyl)-C(R⁵)₂-ψ, -C(R⁵)₂C(R⁶)=C(R⁶)-ψ,
 3 -C(R⁶)=C(R⁶)C(R⁵)₂-ψ, or -C(R⁶)=C(R⁶)-ψ.

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- 1 80. The method of any one of claims 72-76, wherein X is $-(\text{CH}_2)_3-\psi$.
- 1 81. The method of claim 80, wherein R^2 is attached to the 7-position of the tetrahydroquinoline
2 ring.
- 1 82. The method of any one of claims 72-76, wherein X is $-\text{C}(\text{O})-[\text{C}(\text{R}^6)_2]_m-\psi$.
- 1 83. The method of any one of claims 72-82, wherein R^2 is $-\text{N}(\text{R}^7)\text{C}(\text{O})\text{R}^8$.
- 1 84. The method of any one of claims 72-83, wherein R^8 is aryl substituted with 1, 2, or 3
2 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, and C_{1-}
3 ψ haloalkyl.
- 1 85. The method of any one of claims 72-83, wherein R^8 is phenyl substituted with 1, 2, or 3
2 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, and C_{1-}
3 ψ haloalkyl.
- 1 86. The method of any one of claims 72-84, wherein the disorder is rheumatoid arthritis,
2 psoriasis, chronic graft-versus-host disease, acute graft-versus-host disease, Crohn's
3 disease, inflammatory bowel disease, multiple sclerosis, psoriasis, systemic lupus
4 erythematosus, Celiac Sprue, idiopathic thrombocytopenic thrombotic purpura, myasthenia
5 gravis, Sjogren's syndrome, scleroderma, ulcerative colitis, asthma, or epidermal
6 hyperplasia.
- 1 87. The method of any one of claims 72-84, wherein the disorder is cartilage inflammation,
2 bone degradation, arthritis, juvenile arthritis, juvenile rheumatoid arthritis, pauciarticular
3 juvenile rheumatoid arthritis, polyarticular juvenile rheumatoid arthritis, systemic onset
4 juvenile rheumatoid arthritis, juvenile ankylosing spondylitis, juvenile enteropathic arthritis,
5 juvenile reactive arthritis, juvenile Reter's Syndrome, SEA Syndrome, juvenile
6 dermatomyositis, juvenile psoriatic arthritis, juvenile scleroderma, juvenile systemic lupus
7 erythematosus, juvenile vasculitis, pauciarticular rheumatoid arthritis, polyarticular
8 rheumatoid arthritis, systemic onset rheumatoid arthritis, ankylosing spondylitis,
9 enteropathic arthritis, reactive arthritis, Reter's Syndrome, dermatomyositis, psoriatic
10 arthritis, vasculitis, myolitis, polymyolitis, dermatomyolitis, osteoarthritis, polyarteritis
11 nodossa, Wegener's granulomatosis, arteritis, polymyalgia rheumatica, sarcoidosis,
12 sclerosis, primary biliary sclerosis, sclerosing cholangitis, dermatitis, atopic dermatitis,
13 atherosclerosis, Still's disease, chronic obstructive pulmonary disease, Guillain-Barre
14 disease, Type I diabetes mellitus, Graves' disease, Addison's disease, Raynaud's

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- 15 phenomenon, autoimmune hepatitis, psoriatic epidermal hyperplasia, plaque psoriasis,
16 guttate psoriasis, inverse psoriasis, pustular psoriasis, erythrodermic psoriasis, or an
17 immune disorder associated with or arising from activity of pathogenic lymphocytes.
- 1 88. The method of any one of claims 72-85, wherein the disorder is rheumatoid arthritis.
- 1 89. A method of reducing the amount of IL-17 in a subject, comprising administering to a
2 subject an effective amount of a compound of any one of claims 1-36 or 55-70 or a
3 pharmaceutical composition of any one of claims 37-54 or 71 to reduce the amount of IL-17
4 in the subject.
- 1 90. The method of any one of claims 72-89, wherein the subject is a human.
- 1 91. A method of inhibiting the activity of ROR γ , comprising exposing a ROR γ to an effective
2 amount of a compound of any one of claims 1-36 or 55-70 or a pharmaceutical composition
3 of any one of claims 37-54 or 71 to inhibit the activity of said ROR γ .