



- (51) **International Patent Classification:**  
*A61K 31/155* (2006.01) *C07D 231/54* (2006.01)  
*A61P 9/00* (2006.01)
- (21) **International Application Number:**  
PCT/US2013/044734
- (22) **International Filing Date:**  
7 June 2013 (07.06.2013)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**  
61/657,199 8 June 2012 (08.06.2012) US
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- (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, BN, 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, 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, PA, 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, 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, KM, ML, MR, NE, SN, TD, TG).

**Published:**

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) **Title:** INDAZOLE GUANIDINE F<sub>1</sub>F<sub>0</sub>-ATPASE INHIBITORS AND THERAPEUTIC USES THEREOF

(57) **Abstract:** The invention provides indazole guanidine compounds that inhibit F<sub>1</sub>F<sub>0</sub>-ATPase, and methods of using indazole guanidine compounds as therapeutic agents to treat medical disorders, such as an immune disorder, inflammatory condition, or cancer.



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## INDAZOLE GUANIDINE $F_1F_0$ -ATPASE INHIBITORS AND THERAPEUTIC USES THEREOF

### CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to United States Provisional Patent Application serial number 61/657,199, filed June 8, 2012, the contents of which are hereby incorporated by reference.

### FIELD OF THE INVENTION

[0002] The invention provides inhibitors of  $F_1F_0$ -ATPases (e.g., mitochondrial  $F_1F_0$ -ATPases) and their therapeutic use. In particular, the invention provides indazole guanidine compounds that inhibit  $F_1F_0$ -ATPase, and methods of using indazole guanidine compounds as therapeutic agents to treat a number of medical conditions.

### BACKGROUND

[0003] Multicellular organisms exert precise control over cell number. A balance between cell proliferation and cell death achieves this homeostasis. Cell death occurs in nearly every type of vertebrate cell via necrosis or through a suicidal form of cell death, known as apoptosis. Apoptosis is triggered by a variety of extracellular and intracellular signals that engage a common, genetically programmed death mechanism.

[0004] Multicellular organisms use apoptosis to instruct damaged or unnecessary cells to destroy themselves for the good of the organism. Control of the apoptotic process therefore is very important to normal development, for example, fetal development of fingers and toes requires the controlled removal, by apoptosis, of excess interconnecting tissues, as does the formation of neural synapses within the brain. Similarly, controlled apoptosis is responsible for the sloughing off of the inner lining of the uterus (the endometrium) at the start of menstruation. While apoptosis plays an important role in tissue sculpting and normal cellular maintenance, it is also a component of the primary defense against cells and invaders (e.g., viruses) which threaten the well being of the organism.

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[0005] Not surprisingly many diseases are associated with dysregulation of apoptotic cell death. Experimental models have established a cause-effect relationship between aberrant apoptotic regulation and the pathogenicity of various neoplastic, autoimmune and viral diseases. For instance, in the cell-mediated immune response, effector cells (*e.g.*, cytotoxic T lymphocytes “CTLs”) destroy virus-infected cells by inducing the infected cells to undergo apoptosis. The organism subsequently relies on the apoptotic process to destroy the effector cells when they are no longer needed. Autoimmunity is normally prevented by the CTLs inducing apoptosis in each other and even in themselves. Defects in this process are associated with a variety of immune diseases such as lupus erythematosus and rheumatoid arthritis.

[0006] Multicellular organisms also use apoptosis to instruct cells with damaged nucleic acids (*e.g.*, DNA) to destroy themselves prior to becoming cancerous. Some cancer-causing viruses overcome this safeguard by reprogramming infected (transformed) cells to abort the normal apoptotic process. For example, several human papilloma viruses (HPVs) have been implicated in causing cervical cancer by suppressing the apoptotic removal of transformed cells by producing a protein (E6) which inactivates the p53 apoptosis promoter. Similarly, the Epstein-Barr virus (EBV), the causative agent of mononucleosis and Burkitt's lymphoma, reprograms infected cells to produce proteins that prevent normal apoptotic removal of the aberrant cells thus allowing the cancerous cells to proliferate and to spread throughout the organism.

[0007] Still other viruses destructively manipulate a cell's apoptotic machinery without directly resulting in the development of a cancer. For example, destruction of the immune system in individuals infected with the human immunodeficiency virus (HIV) is thought to progress through infected CD4<sup>+</sup> T cells (about 1 in 100,000) instructing uninfected sister cells to undergo apoptosis.

[0008] Some cancers that arise by non-viral means have also developed mechanisms to escape destruction by apoptosis. Melanoma cells, for instance, avoid apoptosis by inhibiting the expression of the gene encoding Apaf-1. Other cancer cells, especially lung and colon cancer cells, secrete high levels of soluble decoy molecules that inhibit the initiation of CTL mediated clearance of aberrant cells. Faulty regulation of the apoptotic machinery has also been implicated in various degenerative conditions and vascular diseases.

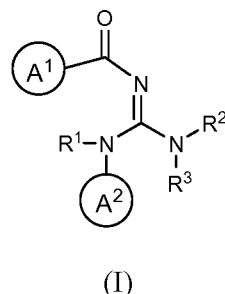
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[0009] Controlled regulation of the apoptotic process and its cellular machinery is important to the survival of multicellular organisms. Typically, the biochemical changes that occur in a cell instructed to undergo apoptosis occur in an orderly procession. However, as shown above, flawed regulation of apoptosis can cause serious deleterious effects in the organism.

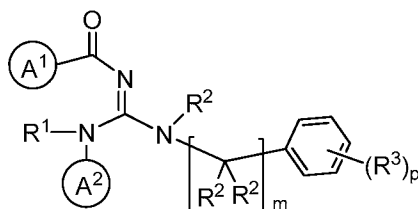
[0010] The need exists for improved compositions and methods for regulating the apoptotic processes in subjects afflicted with diseases and conditions characterized by faulty regulation of these processes (*e.g.*, viral infections, hyperproliferative autoimmune disorders, chronic inflammatory conditions, and cancers). The present invention addresses this need and provides other related advantages.

## SUMMARY

[0011] The invention provides indazole guanidine compounds that inhibit  $F_1F_0$ -ATPase (*e.g.*, mitochondrial  $F_1F_0$ -ATPase), pharmaceutical compositions comprising indazole guanidine compounds, and methods of using such compounds and pharmaceutical compositions to treat a number of medical conditions. Accordingly, one aspect of the invention provides a family of compounds represented by Formula I:



including all stereoisomers, geometric isomers, and tautomers; or a pharmaceutically acceptable salt or solvate of any of the foregoing; wherein the variables are as defined in the detailed description. Another aspect of the invention provides a family of compounds represented by Formula II:



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(II)

including all stereoisomers, geometric isomers, and tautomers; or a pharmaceutically acceptable salt or solvate of any of the foregoing; wherein the variables are as defined in the detailed description. Additional indazole guanidine compounds, e.g., compounds represented  
5 by Formula I-A, Formula I-A1, Formula II-A, Formula II-A1, and Formula III, are described in the detailed description. The foregoing compounds can be present in a pharmaceutical composition comprising a compound described herein and a pharmaceutically acceptable carrier.

[0012] Another aspect of the invention provides a method of treating a subject suffering  
10 from a medical disorder. The method comprises administering to the subject a therapeutically effective amount of one or more indazole guanidine compounds described herein, e.g., a compound of Formula I, I-A, I-A1, II, II-A, II-A1, or III, in order to ameliorate a symptom of the disorder. A large number of disorders can be treated using the indazole guanidine compounds described herein. For example, the compounds described herein can be used to  
15 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 gravis, Sjogren's syndrome, scleroderma, ulcerative colitis, asthma, epidermal hyperplasia, and other medical disorders  
20 described herein. The compounds described herein can also be used to treat a cardiovascular disease, myeloma, lymphoma, cancer, or bacterial infection.

[0013] Another aspect of the invention provides a method of inhibiting a  $F_1F_0$ -ATPase, for example, a mitochondrial  $F_1F_0$ -ATPase. The method comprises exposing the  $F_1F_0$ -ATPase to a compound described herein, such as a compound Formula I, I-A, I-A1, II, II-A, II-A1, or III, to  
25 inhibit said  $F_1F_0$ -ATPase.

#### DETAILED DESCRIPTION OF THE INVENTION

[0014] The invention provides indazole guanidine compounds that inhibit  $F_1F_0$ -ATPase (e.g., mitochondrial  $F_1F_0$ -ATPase), pharmaceutical compositions comprising the indazole guanidine compounds, and methods of using the indazole guanidine compounds and pharmaceutical compositions in therapy.

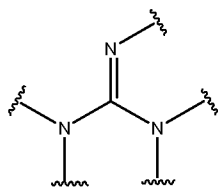
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[0015] Exemplary compositions and methods of the present invention are described in more detail in the following sections: I. Modulators of F<sub>1</sub>F<sub>0</sub>-ATPase Activity; II. Indazole Guanidine Compounds; III. Therapeutic Applications of Indazole Guanidine Compounds, and IV. Pharmaceutical Compositions, Formulations, and Exemplary Administration Routes and Dosing Considerations. Aspects of the invention described in one particular section are not to be limited to any particular section.

[0016] 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, which are within the skill of the art. Such techniques are explained fully in the literature, such as "Comprehensive Organic Synthesis" (B.M. Trost & I. Fleming, eds., 1991-1992); "Molecular cloning: a laboratory manual" Second Edition (Sambrook *et al.*, 1989); "Oligonucleotide synthesis" (M.J. Gait, ed., 1984); "Animal cell culture" (R.I. Freshney, ed., 1987); the series "Methods in enzymology" (Academic Press, Inc.); "Handbook of experimental immunology" (D.M. Weir & C.C. Blackwell, eds.); "Gene transfer vectors for mammalian cells" (J.M. Miller & M.P. Calos, eds., 1987); "Current protocols in molecular biology" (F.M. Ausubel *et al.*, eds., 1987, and periodic updates); "PCR: the polymerase chain reaction" (Mullis *et al.*, eds., 1994); and "Current protocols in immunology" (J.E. Coligan *et al.*, eds., 1991), each of which is herein incorporated by reference in its entirety.

[0017] To facilitate an understanding of the present invention, a number of terms and phrases are defined below.

[0018] As used herein, the term "guanidine" refers to a compound having the following



core structure: , including pharmaceutically acceptable salt forms.

[0019] The term "alkyl" refers to a saturated straight or branched hydrocarbon, such as a straight or branched group of 1-12, 1-10, or 1-6 carbon atoms, referred to herein as C<sub>1</sub>-C<sub>12</sub>alkyl, C<sub>1</sub>-C<sub>10</sub>alkyl, and C<sub>1</sub>-C<sub>6</sub>alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-

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pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, etc.

5 [0020] The term “alkylene” refers to a diradical of an alkyl group. Exemplary alkylene groups include -CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>-, and -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-.

[0021] The term “haloalkyl” refers to an alkyl group that is substituted with at least one halogen. For example, -CH<sub>2</sub>F, -CHF<sub>2</sub>, -CF<sub>3</sub>, -CH<sub>2</sub>CF<sub>3</sub>, -CF<sub>2</sub>CF<sub>3</sub>, and the like.

10 [0022] The term “hydroxyalkyl” refers to an alkyl group that is substituted with at least one hydroxyl group. In certain embodiments, the hydroxyalkyl group is an alkyl group that is substituted with one hydroxyl group.

[0023] The term “cycloalkyl” refers to a monovalent saturated cyclic, bicyclic, or bridged cyclic (e.g., adamantyl) hydrocarbon group of 3-12, 3-8, 4-8, or 4-6 carbons, referred to herein, e.g., as “C<sub>4-8</sub>cycloalkyl,” derived from a cycloalkane. Exemplary cycloalkyl groups include cyclohexyl, cyclopentyl, cyclobutyl, and cyclopropyl.

15 [0024] The term “aralkyl” refers to an alkyl group substituted with an aryl group.

[0025] The term “heteroaralkyl” refers to an alkyl group substituted with a heteroaryl group.

20 [0026] The term “alkenyl” refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon double bond, such as a straight or branched group of 2-12, 2-10, or 2-6 carbon atoms, referred to herein as C<sub>2</sub>-C<sub>12</sub>alkenyl, C<sub>2</sub>-C<sub>10</sub>alkenyl, and C<sub>2</sub>-C<sub>6</sub>alkenyl, respectively. Exemplary alkenyl groups include, but are not limited to, vinyl, allyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl, 2-propyl-2-butenyl, 4-(2-methyl-3-butene)-pentenyl, etc.

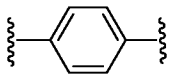
25 [0027] The term “alkynyl” as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon triple bond, such as a straight or branched group of 2-12, 2-8, or 2-6 carbon atoms, referred to herein as C<sub>2</sub>-C<sub>12</sub>alkynyl, C<sub>2</sub>-C<sub>8</sub>alkynyl, and C<sub>2</sub>-C<sub>6</sub>alkynyl, respectively. Exemplary alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, hexynyl, methylpropynyl, 4-methyl-1-butyne, 4-propyl-2-pentyne, and 4-butyl-2-hexynyl, etc.

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[0028] The term "aryl" is art-recognized and refers to a carbocyclic aromatic group.

Representative aryl groups include phenyl, naphthyl, anthracenyl, and the like. Unless 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, -C(O)alkyl, -CO<sub>2</sub>alkyl, carbonyl, carboxyl, alkylthio, sulfonyl, sulfonamido, sulfonamide, ketone, aldehyde, ester, heterocyclyl, heteroaryl, -CF<sub>3</sub>, -CN, or the like. The term "aryl" also includes polycyclic 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 at least one of the rings is aromatic, and the other ring(s) may be, for example, cycloalkyl, cycloalkenyl, cycloalkynyl, and/or aryl. In certain embodiments, the aromatic group is not substituted, i.e., it is unsubstituted.

[0029] 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

indicated. An exemplary arylene group is .

[0030] The terms "heterocyclyl" or "heterocyclic group" are art-recognized and refer to saturated, partially unsaturated, or aromatic 3- to 10-membered ring structures, alternatively 3- to 7-membered rings, whose ring structures include one to four heteroatoms, such as nitrogen, oxygen, and sulfur. Heterocycles may also be mono-, bi-, or other multi-cyclic ring systems. A heterocycle may be fused to one or more aryl, partially unsaturated, or saturated rings.

Heterocyclyl groups include, for example, biotinyl, chromenyl, dihydrofuryl, dihydroindolyl, dihydropyranyl, dihydrothienyl, dithiazolyl, homopiperidinyl, imidazolidinyl, isoquinolyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, oxolanyl, oxazolidinyl, phenoxanthenyl, piperazinyl, piperidinyl, pyranyl, pyrazolidinyl, pyrazolinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidin-2-onyl, pyrrolinyl, tetrahydrofuryl, tetrahydroisoquinolyl, tetrahydropyranyl, tetrahydroquinolyl, thiazolidinyl, thiolanyl, thiomorpholinyl, thiopyranyl, xanthenyl, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, 2,3-dihydrobenzo[d]oxazolyl, and the like. Unless specified otherwise, the heterocyclic ring is optionally substituted at one or more positions with substituents such as alkanoyl, alkoxy, alkyl, alkenyl, alkynyl, amido, amidino, amino, aryl, arylalkyl, azido, carbamate, carbonate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, imino, ketone, nitro, phosphate, phosphonato, phosphinato, sulfate, sulfide, sulfonamido,

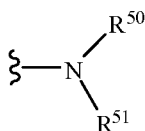
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sulfonyl and thiocarbonyl. In certain embodiments, the heterocyclcyl group is not substituted, i.e., it is unsubstituted.

**[0031]** 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 includes pyrrolyl, furanyl, 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, -CO<sub>2</sub>alkyl, carbonyl, carboxyl, alkylthio, sulfonyl, sulfonamido, sulfonamide, ketone, aldehyde, ester, heterocyclcyl, aryl, -CF<sub>3</sub>, -CN, or the like. The term "heteroaryl" also includes polycyclic 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 at least one of the rings is heteroaromatic, and the other ring(s) may be, for example, cycloalkyl, cycloalkenyl, cycloalkynyl, and/or aryl. Exemplary heteroaryls that have a bicyclic ring system in which two carbon atoms are common to the adjoining ring include, for example, indazolyl, indolyl, and pyrazolo[3,4-c]pyridinyl.

**[0032]** 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.

**[0033]** 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 formula:



wherein R<sup>50</sup> and R<sup>51</sup> each independently represent hydrogen, alkyl, alkenyl, or -(CH<sub>2</sub>)<sub>m</sub>-R<sup>61</sup>; or R<sup>50</sup> and R<sup>51</sup>, taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure; wherein R<sup>61</sup> is aryl, cycloalkyl, cycloalkenyl, a heterocycle or a polycycle; and m is zero or an integer in the range of 1 to 8. In certain embodiments, R<sup>50</sup> and R<sup>51</sup> each independently represent hydrogen or alkyl.

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[0034] The terms “alkoxyl” or “alkoxy” are art-recognized and refer to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, 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 alkoxyl, such as may be represented by one of -O-alkyl, -O-alkenyl, -O-alkynyl, -O-(CH<sub>2</sub>)<sub>m</sub>-R<sup>61</sup>, where m and R<sup>61</sup> are described above.

[0035] The term “amide” or “amido” as used herein refers to a radical of the form -R<sub>a</sub>C(O)N(R<sub>b</sub>)-, -R<sub>a</sub>C(O)N(R<sub>b</sub>)R<sub>c</sub>-, -C(O)NR<sub>b</sub>R<sub>c</sub>, or -C(O)NH<sub>2</sub>, wherein R<sub>a</sub>, R<sub>b</sub> and R<sub>c</sub> are each independently selected from alkoxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, ketone, and nitro. The amide can be attached to another group through the carbon, the nitrogen, R<sub>b</sub>, R<sub>c</sub>, or R<sub>a</sub>. The amide also may be cyclic, for example R<sub>b</sub> and R<sub>c</sub>, R<sub>a</sub> and R<sub>b</sub>, or R<sub>a</sub> and R<sub>c</sub> may be joined to form a 3- to 12-membered ring, such as a 3- to 10-membered ring or a 5- to 6-membered ring. The term “carboxamido” refers to the structure -C(O)NR<sub>b</sub>R<sub>c</sub>.

[0036] The term “sulfonamide” or “sulfonamido” as used herein refers to a radical having the structure -N(R<sub>F</sub>)-S(O)<sub>2</sub>-R<sub>S</sub>- or -S(O)<sub>2</sub>-N(R<sub>F</sub>)R<sub>S</sub>, where R<sub>F</sub> and R<sub>S</sub> can be, for example, hydrogen, alkyl, aryl, cycloalkyl, and heterocyclyl. Exemplary sulfonamides include alkylsulfonamides (e.g., where R<sub>S</sub> is alkyl), arylsulfonamides (e.g., where R<sub>S</sub> is aryl), cycloalkyl sulfonamides (e.g., where R<sub>S</sub> is cycloalkyl), and heterocyclyl sulfonamides (e.g., where R<sub>S</sub> is heterocyclyl), etc.

[0037] The term “sulfonyl” as used herein refers to a radical having the structure R<sub>U</sub>SO<sub>2</sub>-, where R<sub>U</sub> can be alkyl, aryl, cycloalkyl, and heterocyclyl, e.g., alkylsulfonyl. The term “alkylsulfonyl” as used herein refers to an alkyl group attached to a sulfonyl group.

[0038] The symbol “~” indicates a point of attachment.

[0039] The compounds of the disclosure may contain one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers (such as enantiomers, mixtures of enantiomers, diastereomers, and mixtures of diastereomers) and geometric isomers (e.g., an *E*-isomer, *Z*-isomer, or mixture of *E*- and *Z*-isomers). These compounds may be designated by the symbols “R” or “S,” depending on the configuration of substituents around the stereogenic

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carbon atom. Stereoisomers include enantiomers, mixtures of enantiomers, diastereomers, and mixtures of diastereomers. Mixtures of enantiomers or diastereomers may be designated “(±)” in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly. Unless indicated otherwise, generic chemical structures and graphical representations of specific compounds encompass all stereoisomers and geometric isomers.

[0040] Individual stereoisomers of compounds of the present invention can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, or (3) direct separation of the mixture of optical enantiomers on chiral chromatographic columns. Stereoisomeric mixtures can also be resolved into their component stereoisomers by well known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Stereoisomers can also be obtained from stereomerically-pure intermediates, reagents, and catalysts by well known asymmetric synthetic methods.

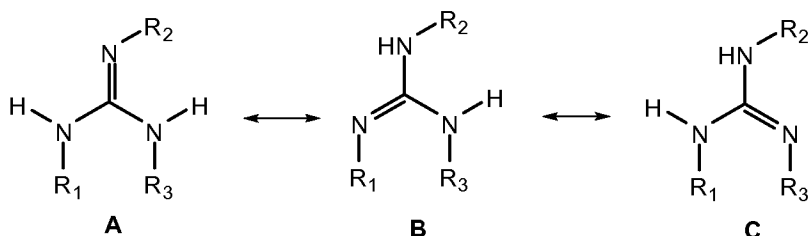
[0041] As indicated above, the invention encompasses the various geometric isomers and mixtures thereof resulting from the arrangement of substituents around a carbon-carbon double bond or arrangement of substituents around a carbocyclic ring. Substituents around a carbon-carbon double bond are designated as being in the “*Z*” or “*E*” configuration wherein the terms “*Z*” and “*E*” are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting double bonds encompass both the “*E*” and “*Z*” isomers.

[0042] Substituents around a carbon-carbon double bond alternatively can be referred to as “*cis*” or “*trans*,” where “*cis*” represents substituents on the same side of the double bond and “*trans*” represents substituents on opposite sides of the double bond. The arrangement of substituents around a carbocyclic ring are designated as “*cis*” or “*trans*.” The term “*cis*” represents substituents on the same side of the plane of the ring and the term “*trans*” represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the

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substituents are disposed on both the same and opposite sides of plane of the ring are designated "cis/trans."

[0043] Certain compounds described herein may exist as a single tautomer or as a mixture of tautomers. For example, certain guanidine compounds having a hydrogen atom attached to at least one of the guanidine nitrogen atoms can exist as a single tautomer or a mixture of tautomers. To illustrate, depending upon the substituents attached at the  $R^1$ ,  $R^2$  and  $R^3$  positions, the guanidine compound may exist as a single tautomer represented by **A**, **B**, or **C**, or as mixture of two or more of **A**, **B**, and **C**.



[0044] The compounds disclosed herein can exist in solvated as well as unsolvated 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.

[0045] The invention also embraces isotopically labeled compounds of the invention which are identical to those recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as  $^2\text{H}$ ,  $^3\text{H}$ ,  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{15}\text{N}$ ,  $^{18}\text{O}$ ,  $^{17}\text{O}$ ,  $^{31}\text{P}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{18}\text{F}$ , and  $^{36}\text{Cl}$ , respectively.

[0046] Certain isotopically-labeled disclosed compounds (*e.g.*, those labeled with  $^3\text{H}$  and  $^{14}\text{C}$ ) are useful in compound and/or substrate tissue distribution assays. Tritiated (*i.e.*,  $^3\text{H}$ ) and carbon-14 (*i.e.*,  $^{14}\text{C}$ ) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (*i.e.*,  $^2\text{H}$ ) may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the invention can generally be prepared by following procedures analogous to those disclosed in the *e.g.*, Examples herein, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

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[0047] The term "IC<sub>50</sub>" is art-recognized and refers to the concentration of a compound that is required for 50% inhibition of its target.

[0048] The term "EC<sub>50</sub>" is art-recognized and refers to the concentration of a compound at which 50% of its maximal effect is observed.

5 [0049] The terms "subject" and "patient" 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. In the context of the invention, the terms "subject" and "patient" generally refer to an individual who will receive or who has received treatment (*e.g.*,  
10 administration of a compound of the present invention and optionally one or more other agents) for a condition characterized by the dysregulation of apoptotic processes.

[0050] As used herein, the term "effective amount" refers to the amount of a compound sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations, applications or dosages and is not intended to be limited to a  
15 particular formulation or administration route. As used herein, the term "treating" includes any effect, *e.g.*, lessening, reducing, modulating, ameliorating or eliminating, that results in the improvement of the condition, disease, disorder, and the like, or ameliorating a symptom thereof.

[0051] The phrase "pathologically proliferating or growing cells" refers to a localized  
20 population of proliferating cells in an animal that is not governed by the usual limitations of normal growth.

[0052] As used herein, the term "un-activated target cell" refers to a cell that is either in the G<sub>0</sub> phase or one to which a stimulus has not been applied.

[0053] As used herein, the term "activated target lymphoid cell" refers to a lymphoid cell  
25 that has been primed with an appropriate stimulus to cause a signal transduction cascade, or alternatively, a lymphoid cell that is not in G<sub>0</sub> phase. Activated lymphoid cells may proliferate, undergo activation induced cell death, or produce one or more cytotoxins, cytokines, or other related membrane-associated proteins characteristic of the cell type (*e.g.*, CD8<sup>+</sup> or CD4<sup>+</sup>). They are also capable of recognizing and binding any target cell that displays a particular  
30 antigen on its surface, and subsequently releasing its effector molecules.

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[0054] As used herein, the term "activated cancer cell" refers to a cancer cell that has been primed with an appropriate stimulus to cause signal transduction. An activated cancer cell may or may not be in the G<sub>0</sub> phase.

[0055] An activating agent is a stimulus that upon interaction with a target cell results in a signal transduction cascade. Examples of activating stimuli include, but are not limited to, small molecules, radiant energy, and molecules that bind to cell activation cell surface receptors. Responses induced by activation stimuli can be characterized by changes in, among others, intracellular Ca<sup>2+</sup>, superoxide, or hydroxyl radical levels; the activity of enzymes like kinases or phosphatases; or the energy state of the cell. For cancer cells, activating agents also include transforming oncogenes.

[0056] As used herein, the term "dysregulation of the process of cell death" refers to any aberration in the ability (*e.g.*, predisposition) of a cell to undergo cell death via either necrosis or apoptosis. Dysregulation of cell death is associated with or induced by a variety of conditions, including for example, immune disorders (*e.g.*, systemic lupus erythematosus, autoimmune disorders, rheumatoid arthritis, graft-versus-host disease, myasthenia gravis, Sjögren's syndrome, *etc.*), chronic inflammatory conditions (*e.g.*, psoriasis, asthma and Crohn's disease), hyperproliferative disorders (*e.g.*, tumors, B cell lymphomas, T cell lymphomas, *etc.*), viral infections (*e.g.*, herpes, papilloma, HIV), and other conditions such as osteoarthritis and atherosclerosis.

[0057] It should be noted that when the dysregulation is induced by or associated with a viral infection, the viral infection may or may not be detectable at the time dysregulation occurs or is observed. That is, viral-induced dysregulation can occur even after the disappearance of symptoms of viral infection.

[0058] A "hyperproliferative disorder," as used herein refers to any condition in which a localized population of proliferating cells in an animal is not governed by the usual limitations of normal growth. Examples of hyperproliferative disorders include tumors, neoplasms, lymphomas and the like. A neoplasm is said to be benign if it does not undergo invasion or metastasis and malignant if it does either of these. A metastatic cell or tissue means that the cell can invade and destroy neighboring body structures. Hyperplasia is a form of cell proliferation involving an increase in cell number in a tissue or organ, without significant alteration in structure or function. Metaplasia is a form of controlled cell growth in which one

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type of fully differentiated cell substitutes for another type of differentiated cell. Metaplasia can occur in epithelial or connective tissue cells. A typical metaplasia involves a somewhat disorderly metaplastic epithelium.

**[0059]** The pathological growth of activated lymphoid cells often results in an immune disorder or a chronic inflammatory condition. As used herein, the term “immune disorder” refers to any condition in which an organism produces antibodies or immune cells which recognize the organism's own molecules, cells or tissues. Non-limiting examples of immune disorders include autoimmune disorders, immune hemolytic anemia, immune hepatitis, Berger's disease or IgA nephropathy, Celiac Sprue, chronic fatigue syndrome, Crohn's disease, dermatomyositis, fibromyalgia, graft-versus-host disease, Grave's disease, Hashimoto's thyroiditis, idiopathic thrombocytopenia purpura, lichen planus, multiple sclerosis, myasthenia gravis, psoriasis, rheumatic fever, rheumatic arthritis, scleroderma, Sjorgren syndrome, systemic lupus erythematosus, type 1 diabetes, ulcerative colitis, vitiligo, tuberculosis, and the like.

**[0060]** As used herein, the term “chronic inflammatory condition” refers to a condition wherein the organism's immune cells are activated. Such a condition is characterized by a persistent inflammatory response with pathologic sequelae. This state is characterized by infiltration of mononuclear cells, proliferation of fibroblasts and small blood vessels, increased connective tissue, and tissue destruction. Examples of chronic inflammatory diseases include, but are not limited to, Crohn's disease, psoriasis, chronic obstructive pulmonary disease, inflammatory bowel disease, multiple sclerosis, and asthma. Immune diseases such as rheumatoid arthritis and systemic lupus erythematosus can also result in a chronic inflammatory state.

**[0061]** As used herein, the term “co-administration” refers to the administration of at least two agent(s) (*e.g.*, a compound of the present invention) or therapies to a subject. In some embodiments, the co-administration of two or more agents/therapies is concurrent. In other embodiments, a first agent/therapy is administered prior to a second agent/therapy. Those of skill in the art understand that the formulations and/or routes of administration of the various agents/therapies used may vary. The appropriate dosage for co-administration can be readily determined by one skilled in the art. In some embodiments, when agents/therapies are co-administered, the respective agents/therapies are administered at lower dosages than

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appropriate for their administration alone. Thus, co-administration is especially desirable in embodiments where the co-administration of the agents/therapies lowers the requisite dosage of a known potentially harmful (*e.g.*, toxic) agent(s).

5 [0062] 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*.

10 [0063] 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., Mack Publ. Co., Easton, PA [1975].

15 [0064] 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 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, 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.

25 [0065] 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<sub>1-4</sub> alkyl, and the like.

30 [0066] 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,

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hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, undecanoate, and the like. Other examples of salts include anions of the compounds of the present invention compounded  
5 with a suitable cation such as  $\text{Na}^+$ ,  $\text{NH}_4^+$ , and  $\text{NW}_4^+$  (wherein W is a  $\text{C}_{1-4}$  alkyl group), and the like.

[0067] 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  
10 purification of a pharmaceutically acceptable compound.

[0068] As used herein, the term “modulate” refers to the activity of a compound (*e.g.*, a compound of the present invention) to affect (*e.g.*, to promote or retard) an aspect of cellular function, including, but not limited to, cell growth, proliferation, apoptosis, and the like.

[0069] 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.  
15

[0070] As a general matter, compositions specifying a percentage are by weight unless otherwise specified. Further, if a variable is not accompanied by a definition, then the previous definition of the variable controls.  
20

#### **I. Modulators of $\text{F}_1\text{F}_0$ -ATPase Activity**

[0071] In some embodiments, the present invention regulates  $\text{F}_1\text{F}_0$ -ATPase activity (*e.g.*,  
25 mitochondrial  $\text{F}_1\text{F}_0$ -ATPase activity) through the exposure of cells to compounds of the present invention. In some embodiments, the compounds inhibit ATP synthesis and ATP hydrolysis. The effect of the compounds can be measured by detecting any number of cellular changes. For example, mitochondrial  $\text{F}_1\text{F}_0$ -ATPase activity and/or cell death may be assayed as described herein and in the art. In some embodiments, cell lines are maintained under  
30 appropriate cell culturing conditions (*e.g.*, gas ( $\text{CO}_2$ ), temperature and media) for an

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appropriate period of time to attain exponential proliferation without density dependent constraints. Cell number and or viability are measured using standard techniques, such as trypan blue exclusion/hemo-cytometry, or an Alamar Blue or MTT dye conversion assay. Alternatively, the cell may be analyzed for the expression of genes or gene products associated with aberrations in apoptosis or necrosis.

[0072] In some embodiments, exposing the compounds of the present invention to a cell induces apoptosis. In some embodiments, the present invention induces apoptosis or arrest of cell proliferation through interacting with the mitochondrial  $F_1F_0$ -ATPase. In some embodiments, the compounds of the present invention inhibit mitochondrial  $F_1F_0$ -ATPase activity through binding the OSCP. In some embodiments, the compounds of the present invention bind the junction between the OSCP and the  $F_1$  subunit of the mitochondrial  $F_1F_0$ -ATPase. In some embodiments, the compounds of the present invention bind the  $F_1$  subunit. In certain embodiments, screening assays of the present invention permit detection of binding partners of the OSCP,  $F_1$ , or OSCP/ $F_1$  junction.

[0073] In some embodiments, exposing a compound of the present invention to a cell induces apoptosis. In some embodiments, the present invention causes an initial increase in cellular ROS levels (*e.g.*,  $O_2^-$ ). In further embodiments, exposure of the compounds of the present invention to a cell causes an increase in cellular  $O_2^-$  levels. In still further embodiments, the increase in cellular  $O_2^-$  levels resulting from the compounds of the present invention is detectable with a redox-sensitive agent that reacts specifically with  $O_2^-$  (*e.g.*, dihydroethidium (DHE)).

[0074] In some embodiments, the present invention causes a collapse of a cell's mitochondrial transmembrane potential ( $\Delta\Psi_m$ ). In some embodiments, a collapse of a cell's mitochondrial  $\Delta\Psi_m$  resulting from the present invention is detectable with a mitochondria-selective potentiometric probe (*e.g.*, *3,3'-Dihexyloxacarbocyanine iodide*, DiOC<sub>6</sub>). In further embodiments, a collapse of a cell's mitochondrial  $\Delta\Psi_m$  resulting from the present invention occurs after an initial increase in cellular  $O_2^-$  levels.

[0075] In some embodiments, the present invention enables caspase activation. In other embodiments, the present invention causes the release of cytochrome *c* from mitochondria. In further embodiments, the present invention alters cytosolic cytochrome *c* levels. In still other embodiments, altered cytosolic cytochrome *c* levels resulting from the present invention are

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detectable by immunoblotting cytosolic fractions. In some embodiments, diminished cystolic cytochrome *c* levels resulting from the present invention are detectable after a period of time (*e.g.*, 10 hours). In further preferred embodiments, diminished cystolic cytochrome *c* levels resulting from the present invention are detectable after 5 hours.

- 5 [0076] In other embodiments, the present invention causes the opening of the mitochondrial permeability transition pore. In some embodiments, the cellular release of cytochrome *c* resulting from the present invention is consistent with a collapse of mitochondrial  $\Delta\Psi_m$ . In still further embodiments, the present invention causes an increase in cellular  $O_2^-$  levels after a mitochondrial  $\Delta\Psi_m$  collapse and a release of cytochrome *c*. In further embodiments, a rise in  
10 cellular  $O_2^-$  levels is caused by a mitochondrial  $\Delta\Psi_m$  collapse and release of cytochrome *c* resulting from the present invention.

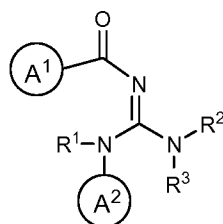
- [0077] In other embodiments, the present invention causes cellular caspase activation. In some embodiments, caspase activation resulting from the present invention is measurable with a pan-caspase sensitive fluorescent substrate (*e.g.*, FAM-VAD-fmk). In still further  
15 embodiments, caspase activation resulting from the present invention tracks with a collapse of mitochondrial  $\Delta\Psi_m$ . In other embodiments, the present invention causes an appearance of hypodiploid DNA. In some embodiments, an appearance of hypodiploid DNA resulting from the present invention is slightly delayed with respect to caspase activation.

- [0078] In some embodiments, the molecular target for the present invention is found within  
20 mitochondria. In further embodiments, the molecular target of the present invention involves the mitochondrial ATPase. The primary sources of cellular ROS include redox enzymes and the mitochondrial respiratory chain (hereinafter MRC). In some embodiments, cytochrome *c* oxidase (complex IV of the MRC) inhibitors (*e.g.*,  $NaN_3$ ) preclude a present invention dependent increase in cellular ROS levels. In other embodiments, the ubiquinol-cytochrome *c*  
25 reductase component of MRC complex III inhibitors (*e.g.*, FK506) preclude a present invention dependent increase in ROS levels.

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## II. Indazole Guanidine Compounds

[0079] One aspect of the invention provides a family of compounds represented by Formula I:

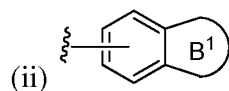


(I)

including all stereoisomers, geometric isomers, and tautomers; or a pharmaceutically acceptable salt or solvate of any of the foregoing; wherein:

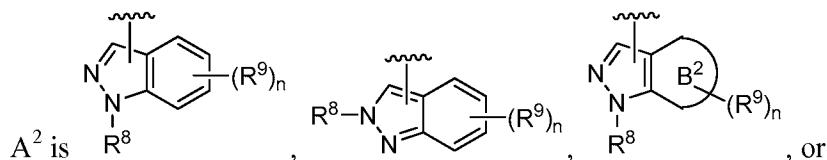
A<sup>1</sup> is one of the following:

- (i) phenyl or a six-membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, cyano, -CO<sub>2</sub>R<sup>4</sup>, -C(O)R<sup>5</sup>, -S(O)R<sup>5</sup>, -SO<sub>2</sub>R<sup>5</sup>, -SO<sub>2</sub>N(R<sup>6</sup>)(R<sup>7</sup>), -C(O)N(R<sup>6</sup>)(R<sup>7</sup>), -N(R<sup>6</sup>)(R<sup>7</sup>), and -N(R<sup>4</sup>)C(O)(R<sup>5</sup>); or



that is optionally substituted with 1 or 2 substituents

independently selected from the group consisting of halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, and C<sub>1</sub>-C<sub>6</sub>alkoxy; wherein B<sup>1</sup> is a 5-membered or 6-membered heterocycle;



; wherein B<sup>2</sup> is a 6-membered heteroaromatic group;

R<sup>1</sup> and R<sup>2</sup> each represent independently hydrogen or alkyl;

R<sup>3</sup> is one of the following:

- (i) alkyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of hydroxyl, alkoxy, -O-(C(R<sup>4</sup>)<sub>2</sub>)<sub>m</sub>-alkoxy,

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-O-(C(R<sup>4</sup>)<sub>2</sub>)<sub>m</sub>-OH, -N(R<sup>6</sup>)(R<sup>7</sup>), cycloalkyl, heterocycloalkyl, -N(R<sup>6</sup>)C(O)R<sup>8</sup>,  
-C(O)N(R<sup>6</sup>)(R<sup>7</sup>), -N(R<sup>6</sup>)C(O)N(R<sup>6</sup>)(R<sup>7</sup>), halogen, haloalkyl, and cyano; or

(ii) cycloalkyl or heterocycloalkyl, each of which is optionally substituted with  
1, 2, or 3 substituents independently selected from the group consisting of  
halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl, hydroxyalkyl, alkoxy,  
-O-(C(R<sup>4</sup>)<sub>2</sub>)<sub>m</sub>-alkoxyl, -O-(C(R<sup>4</sup>)<sub>2</sub>)<sub>m</sub>-OH, and cyano;

R<sup>4</sup> represents independently for each occurrence hydrogen, alkyl, or cycloalkyl; or two  
occurrences of R<sup>4</sup> attached to the same carbon atom are taken together with said carbon atom to  
form a saturated carbocyclic ring;

R<sup>5</sup> represents independently for each occurrence alkyl or cycloalkyl;

R<sup>6</sup> and R<sup>7</sup> each represent independently for each occurrence hydrogen, alkyl, or  
cycloalkyl; or R<sup>6</sup> and R<sup>7</sup> are taken together with the nitrogen atom to which they are attached to  
form a 3 to 7 membered heterocyclic ring optionally substituted with 1, 2, or 3 substituents  
independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl,  
cycloalkyl, and C<sub>1</sub>-C<sub>6</sub>alkoxy;

R<sup>8</sup> is hydrogen, or R<sup>8</sup> is alkyl substituted by hydroxyl, -N(H)(R<sup>6</sup>), heterocycloalkyl,  
-N(H)C(O)R<sup>10</sup>, -C(O)N(H)(R<sup>6</sup>), or -N(H)C(O)N(R<sup>6</sup>)(R<sup>7</sup>);

R<sup>9</sup> represents independently for each occurrence halogen, haloalkyl, alkyl, cycloalkyl,  
heterocycloalkyl, hydroxyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, or cyano;

R<sup>10</sup> is alkyl, cycloalkyl, aryl, or aralkyl; and

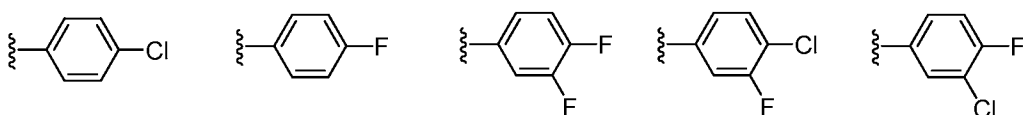
n is 0, 1, 2, 3, or 4; and

m is 1, 2, 3, 4, or 5.

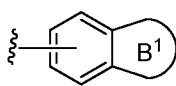
**[0080]** Definitions of the variables in Formula I above encompass multiple chemical  
groups. The application contemplates embodiments where, for example, i) the definition of a  
variable is a single chemical group selected from those chemical groups set forth above, ii) the  
definition is a collection 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 which the variables  
are defined by (i) or (ii), e.g., such as where A<sup>1</sup> is phenyl or a six-membered heteroaryl, each of  
which is optionally substituted with 1, 2, or 3 substituents independently selected from the  
group consisting of halogen and haloalkyl, R<sup>1</sup> is hydrogen, R<sup>2</sup> is hydrogen, R<sup>3</sup> is alkyl, and n is  
1 or 2.

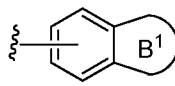
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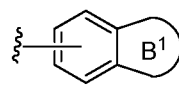
[0081] In certain embodiments, A<sup>1</sup> is phenyl or a six-membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, and C<sub>1</sub>-C<sub>6</sub>alkoxy. In certain other embodiments, A<sup>1</sup> is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, and hydroxyl. In certain other embodiments, A<sup>1</sup> is phenyl substituted with 1 or 2 substituents independently selected from the group consisting of chloro, fluoro, and trifluoromethyl. In certain other embodiments, A<sup>1</sup> is phenyl substituted with 1 or 2 substituents independently selected from the group consisting of chloro and fluoro. In certain other embodiments, A<sup>1</sup> is one of the following:



[0082] In certain embodiments, A<sup>1</sup> is a six-membered heteroaryl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, and heterocycloalkyl. In certain other embodiments, A<sup>1</sup> is a six-membered heteroaryl substituted with a heterocycloalkyl. In certain other embodiments, A<sup>1</sup> is pyridinyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, and heterocycloalkyl. In certain other embodiments, A<sup>1</sup> is a pyridinyl substituted with a 6-membered heterocycloalkyl. In certain embodiments, A<sup>1</sup> is a pyridinyl substituted with morpholinyl.

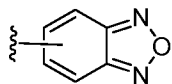
[0083] In certain other embodiments, A<sup>1</sup> is  optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, and C<sub>1</sub>-C<sub>6</sub>alkoxy; wherein B<sup>1</sup> is a 5-membered or 6-

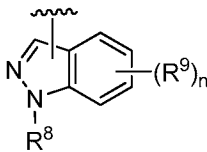
membered heterocycle. In certain other embodiments, A<sup>1</sup> is  optionally substituted with 1 or 2 substituents independently selected from the group consisting of

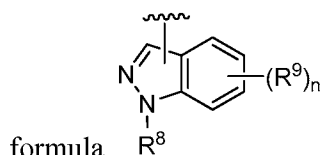
halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, and C<sub>1</sub>-C<sub>6</sub>alkoxy; wherein B<sup>1</sup> is a 5-membered heteroaromatic group. In certain other embodiments, A<sup>1</sup> is 

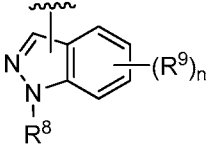
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wherein B<sup>1</sup> is a 5-membered heteroaromatic group. In certain other embodiments, A<sup>1</sup> is

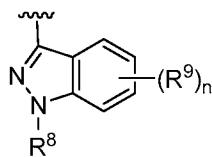


[0084] In certain embodiments, A<sup>2</sup> is . It is understood that the chemical

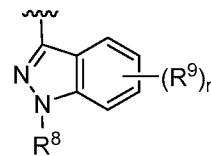
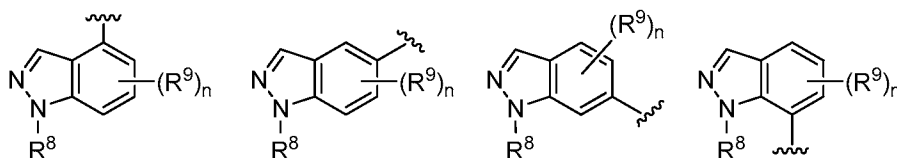


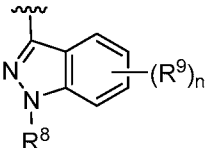
formula  conveys that the indazolyl structure shown can be attached to the

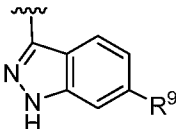
- 5 guanidine core via (i) a carbon atom of the 5-membered ring of the indazolyl structure or (ii) a carbon atom of the 6-membered ring of the indazolyl structure. An example of where the indazolyl is attached to the guanidine core via a carbon atom of the 5-membered ring of the indazolyl structure is depicted below:



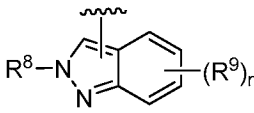
- 10 [0085] Examples of where the indazolyl is attached to the guanidine core via a carbon atom of the 6-membered ring of the indazolyl structure is depicted by the following formulae:

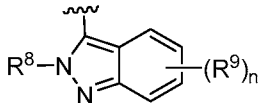


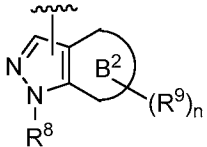
[0086] Accordingly, in certain other embodiments, A<sup>2</sup> is . In certain

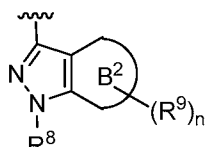
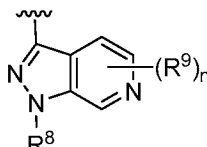
embodiments, A<sup>2</sup> is .

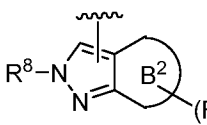
- 23 -

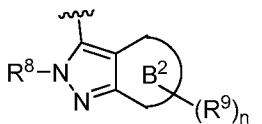
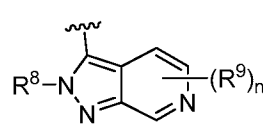
[0087] In certain embodiments,  $A^2$  is . In certain other embodiments,

$A^2$  is .

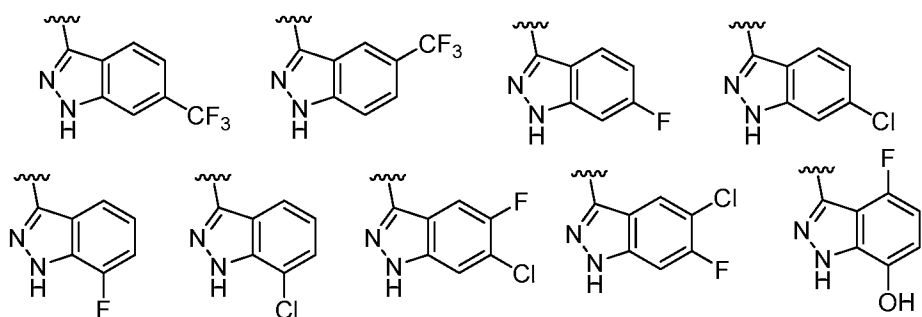
[0088] In certain embodiments,  $A^2$  is . In certain other embodiments,  $A^2$

is . In certain other embodiments,  $A^2$  is .

5 [0089] In certain embodiments,  $A^2$  is . In certain other embodiments,

$A^2$  is . In certain other embodiments,  $A^2$  is .

[0090] In certain embodiments,  $A^2$  is one of the following:



10 [0091] In certain embodiments,  $R^1$  is hydrogen. In certain embodiments,  $R^1$  is alkyl, such as methyl or ethyl. In certain embodiments,  $R^2$  is hydrogen. In certain embodiments,  $R^2$  is alkyl, such as methyl or ethyl. In certain embodiments,  $R^1$  and  $R^2$  are hydrogen.

[0092] In certain embodiments,  $R^3$  alkyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of hydroxyl, alkoxy,  $-O-(C(R^4)_2)_m$ -alkoxy,

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-O-(C(R<sup>4</sup>)<sub>2</sub>)<sub>m</sub>-OH, -N(R<sup>6</sup>)(R<sup>7</sup>), and cycloalkyl. In certain other embodiments, R<sup>3</sup> is alkyl or cycloalkyl. In certain other embodiments, R<sup>3</sup> is cyclobutyl, cyclopentyl, cyclohexyl, or C<sub>2-6</sub> alkyl. In certain other embodiments, R<sup>3</sup> is C<sub>1-6</sub> alkyl substituted by C<sub>1-6</sub> alkoxy. In certain other embodiments, R<sup>3</sup> is alkyl, such as propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, or 2,2-dimethyl-1-propyl.

[0093] In certain embodiments, R<sup>3</sup> is cycloalkyl or heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, and alkyl. In certain other embodiments, R<sup>3</sup> is cycloalkyl substituted by alkyl. In certain other embodiments, R<sup>3</sup> is C<sub>3-6</sub> cycloalkyl substituted by C<sub>1-6</sub> alkyl. In certain other embodiments, R<sup>3</sup> is heterocycloalkyl, such as morpholinyl.

[0094] In certain embodiments, R<sup>4</sup> represents independently for each occurrence hydrogen or methyl. In certain other embodiments, R<sup>4</sup> is hydrogen.

[0095] In certain embodiments, R<sup>5</sup> is hydrogen. In certain embodiments, R<sup>5</sup> is methyl.

[0096] In certain embodiments, R<sup>6</sup> is hydrogen. In certain embodiments, R<sup>6</sup> is alkyl, such as methyl or ethyl. In certain embodiments, R<sup>7</sup> is hydrogen. In certain embodiments, R<sup>7</sup> is alkyl, such as methyl or ethyl. In certain embodiments, R<sup>6</sup> and R<sup>7</sup> are hydrogen.

[0097] In certain embodiments, R<sup>8</sup> is hydrogen.

[0098] In certain embodiments, R<sup>9</sup> represents independently for each occurrence halogen or haloalkyl. In certain other embodiments, R<sup>9</sup> represents independently for each occurrence chloro, fluoro, or trifluoromethyl.

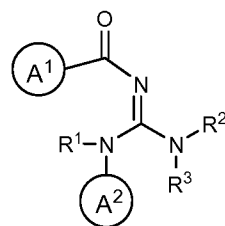
[0099] In certain embodiments, R<sup>10</sup> is alkyl, such as methyl or ethyl.

[00100] In certain embodiments, m is 1 or 2.

[00101] In certain embodiments, n is 1 or 2.

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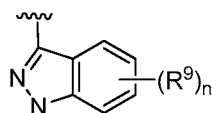
[00102] Another aspect of the invention provides a family of compounds represented by Formula I-A:

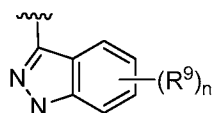


(I-A)

5 including all stereoisomers, geometric isomers, and tautomers; or a pharmaceutically acceptable salt or solvate of any of the foregoing; wherein:

A<sup>1</sup> is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, and hydroxyl;



A<sup>2</sup> is  ;

10 R<sup>1</sup> and R<sup>2</sup> are hydrogen;

R<sup>3</sup> is one of the following:

- (i) alkyl optionally substituted with hydroxyl or alkoxy; or
- (ii) cycloalkyl optionally substituted with hydroxyl, alkyl, cycloalkyl, hydroxyalkyl, or alkoxy;

15 R<sup>8</sup> is hydrogen;

R<sup>9</sup> represents independently for each occurrence halogen, haloalkyl, alkyl, hydroxyl, or C<sub>1</sub>-C<sub>6</sub>alkoxy; and

n is 1 or 2.

[00103] Definitions of the variables in Formula I-A 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 which the variables are defined by (i) or (ii), e.g., such as where A<sup>1</sup> is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen and haloalkyl, R<sup>3</sup> is alkyl

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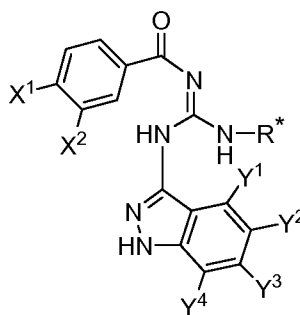
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optionally substituted with hydroxyl or alkoxy, and R<sup>9</sup> represents independently for each occurrence halogen or haloalkyl.

**[00104]** Another aspect of the invention provides a family of compounds represented by

5 Formula I-A1:



(I-A1)

including all stereoisomers, geometric isomers, and tautomers; or a pharmaceutically acceptable salt or solvate of any of the foregoing; wherein:

10 X<sup>1</sup> and X<sup>2</sup> each represent independently hydrogen, chloro, fluoro, or -CF<sub>3</sub>;

Y<sup>1</sup>, Y<sup>2</sup>, Y<sup>3</sup>, and Y<sup>4</sup> each represent independently hydrogen, chloro, fluoro, hydroxyl, or -CF<sub>3</sub>; and

R<sup>\*</sup> is one of the following:

- 15 (i) alkyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of hydroxyl, alkoxy, and cycloalkyl; or
- (ii) cycloalkyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of hydroxyl, alkyl, hydroxyalkyl, and alkoxy.

**[00105]** Definitions of the variables in Formula I-A1 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 which the variables are defined by (i) or (ii), e.g., such as where X<sup>1</sup> and X<sup>2</sup> each represent independently chloro or fluoro, and R<sup>\*</sup> is alkyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of hydroxyl and alkoxy.

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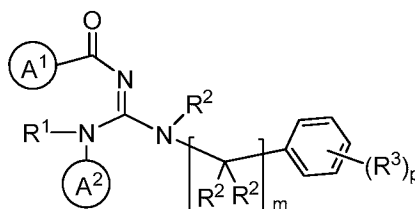
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[00106] Accordingly, in certain embodiments,  $X^1$  and  $X^2$  are each independently chloro or fluoro.

[00107] In certain embodiments,  $Y^1$ ,  $Y^2$ , and  $Y^4$  are hydrogen; and  $Y^3$  is fluoro or  $-CF_3$ . In certain other embodiments,  $Y^1$  and  $Y^4$  are hydrogen; and  $Y^2$  and  $Y^3$  are each independently fluoro or  $-CF_3$ . In certain other embodiments,  $Y^1$  and  $Y^4$  are hydrogen; and  $Y^2$  and  $Y^3$  are each independently fluoro or chloro.

[00108] In certain embodiments,  $R^*$  is alkyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of hydroxyl, alkoxy, and cycloalkyl. In certain other embodiments,  $R^*$  is alkyl or cycloalkyl. In certain other embodiments,  $R^*$  is cyclobutyl, cyclopentyl, cyclohexyl, or  $C_{2-6}$  alkyl. In certain other embodiments,  $R^*$  is  $C_{1-6}$  alkyl substituted by  $C_{1-6}$  alkoxy. In certain other embodiments,  $R^*$  is  $C_{1-6}$  alkyl, such as ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, or tert-butyl.

[00109] Another aspect of the invention provides a family of compounds represented by Formula II:



(II)

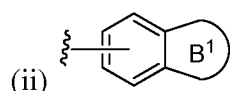
including all stereoisomers, geometric isomers, and tautomers; or a pharmaceutically acceptable salt or solvate of any of the foregoing; wherein:

20  $A^1$  is one of the following:

- (i) phenyl or a six-membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl,  $C_1$ - $C_6$ alkoxy, cyano,  $-CO_2R^4$ ,  $-C(O)R^5$ ,  $-S(O)R^5$ ,  $-SO_2R^5$ ,  $-SO_2N(R^6)(R^7)$ ,  $-C(O)N(R^6)(R^7)$ ,  $-N(R^6)(R^7)$ , and  $-N(R^4)C(O)(R^5)$ ; or

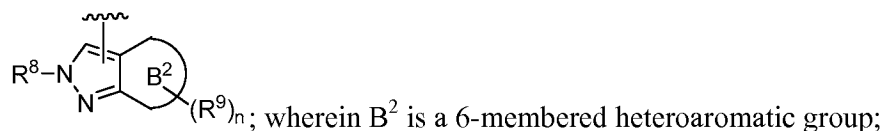
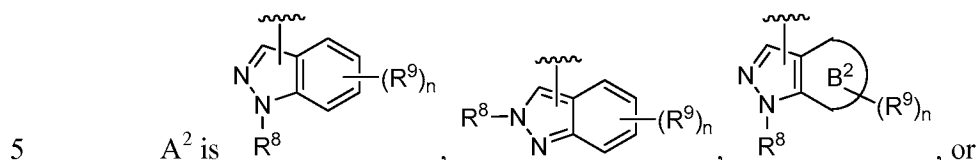
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that is optionally substituted with 1 or 2 substituents

independently selected from the group consisting of halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, and C<sub>1</sub>-C<sub>6</sub>alkoxy; wherein B<sup>1</sup> is a 5- or 6-membered heterocycle;



R<sup>1</sup> is hydrogen or alkyl;

R<sup>2</sup> represents independently for each occurrence hydrogen or alkyl;

R<sup>3</sup> represents independently for each occurrence halogen, haloalkyl, hydroxyl, alkyl,

10 cycloalkyl, heterocycloalkyl, hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, or cyano;

R<sup>4</sup> represents independently for each occurrence hydrogen, alkyl, or cycloalkyl; or two occurrences of R<sup>4</sup> attached to the same carbon atom are taken together with said carbon atom to form a saturated carbocyclic ring;

R<sup>5</sup> represents independently for each occurrence alkyl or cycloalkyl;

15 R<sup>6</sup> and R<sup>7</sup> each represent independently for each occurrence hydrogen, alkyl, or cycloalkyl; or R<sup>6</sup> and R<sup>7</sup> are taken together with the nitrogen atom to which they are attached to form a 3 to 7 membered heterocyclic ring optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl, and C<sub>1</sub>-C<sub>6</sub>alkoxy;

20 R<sup>8</sup> is hydrogen, or R<sup>8</sup> is alkyl substituted by hydroxyl, -N(H)(R<sup>6</sup>), heterocycloalkyl, -N(H)C(O)R<sup>10</sup>, -C(O)N(H)(R<sup>6</sup>), or -N(H)C(O)N(R<sup>6</sup>)(R<sup>7</sup>);

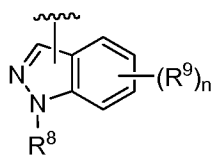
R<sup>9</sup> represents independently for each occurrence halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, or cyano;

R<sup>10</sup> is alkyl, cycloalkyl, aryl, or aralkyl;

25 n is 0, 1, 2, 3, or 4;

m and p each represent independently 0, 1, 2, or 3; and

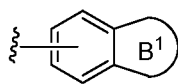
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provided that if  $A^2$  is  $R^8$  and  $R^3$  is halogen or haloalkyl, then  $n$  is 1, 2 or 3.

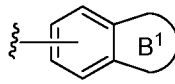
**[00110]** Definitions of the variables in Formula II above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition is a collection 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 which the variables are defined by (i) or (ii), e.g., such as where  $A^1$  is phenyl or a six-membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen and haloalkyl,  $R^1$  is hydrogen,  $R^2$  is hydrogen,  $R^3$  is halogen, and  $n$  is 1 or 2.

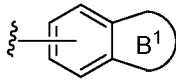
**[00111]** Accordingly, in certain embodiments,  $A^1$  is phenyl or a six-membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, and  $C_1$ - $C_6$ alkoxy. In certain other embodiments,  $A^1$  is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, and hydroxyl. In certain other embodiments,  $A^1$  is phenyl substituted with 1 or 2 substituents independently selected from the group consisting of chloro, fluoro, and trifluoromethyl. In certain other embodiments,  $A^1$  is a six-membered heteroaryl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, and heterocycloalkyl. In certain other embodiments,  $A^1$  is pyridinyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, and heterocycloalkyl. In certain other embodiments,  $A^1$  is a pyridinyl substituted with a 6-membered heterocycloalkyl. In certain other embodiments,  $A^1$  is a pyridinyl substituted with morpholinyl.

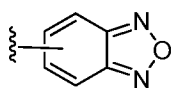


**[00112]** In certain embodiments,  $A^1$  is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, and  $C_1$ - $C_6$ alkoxy; wherein  $B^1$  is a 5-membered or 6-

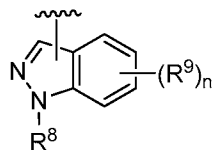
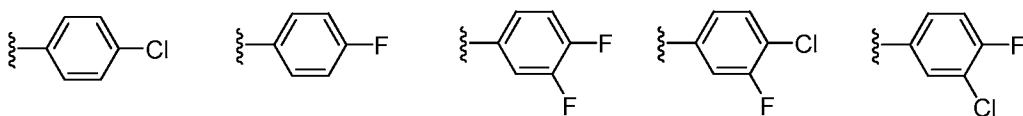
- 30 -

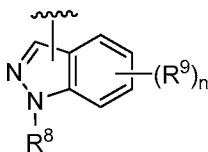
membered heterocycle. In certain other embodiments, A<sup>1</sup> is  optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, and C<sub>1</sub>-C<sub>6</sub>alkoxy; wherein B<sup>1</sup>

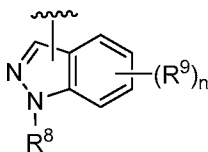
is a 5-membered heteroaromatic group. In certain other embodiments, A<sup>1</sup> is  wherein B<sup>1</sup> is a 5-membered heteroaromatic group. In certain other embodiments, A<sup>1</sup> is

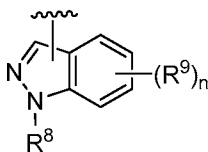


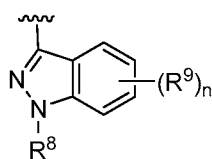
[00113] In certain embodiments, A<sup>1</sup> is one of the following:



[00114] In certain embodiments, A<sup>2</sup> is . It is understood that the chemical



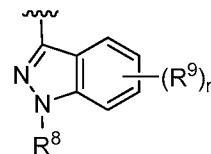
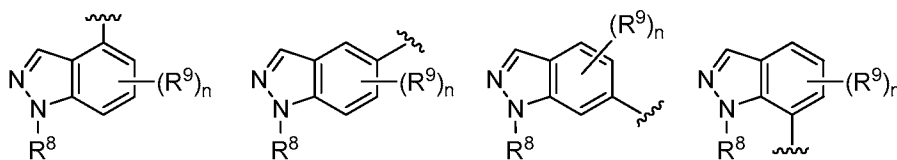
10 formula  conveys that the indazolyl structure shown can be attached to the guanidine core via (i) a carbon atom of the 5-membered ring of the indazolyl structure or (ii) a carbon atom of the 6-membered ring of the indazolyl structure. An example of where the indazolyl is attached to the guanidine core via a carbon atom of the 5-membered ring of the indazolyl structure is depicted below:



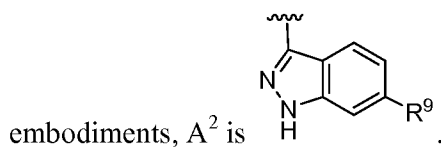
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[00115] Examples of where the indazolyl is attached to the guanidine core via a carbon atom of the 6-membered ring of the indazolyl structure is depicted by the following formulae:

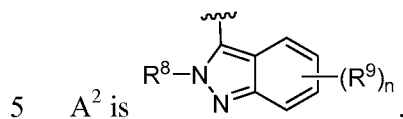
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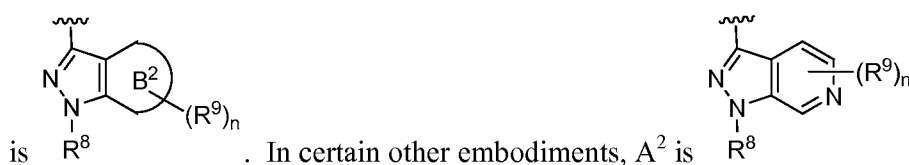
[00116] Accordingly, in certain other embodiments, A<sup>2</sup> is . In certain



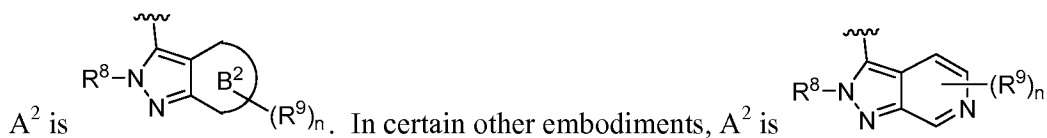
[00117] In certain embodiments, A<sup>2</sup> is . In certain other embodiments,



[00118] In certain embodiments, A<sup>2</sup> is . In certain other embodiments, A<sup>2</sup>

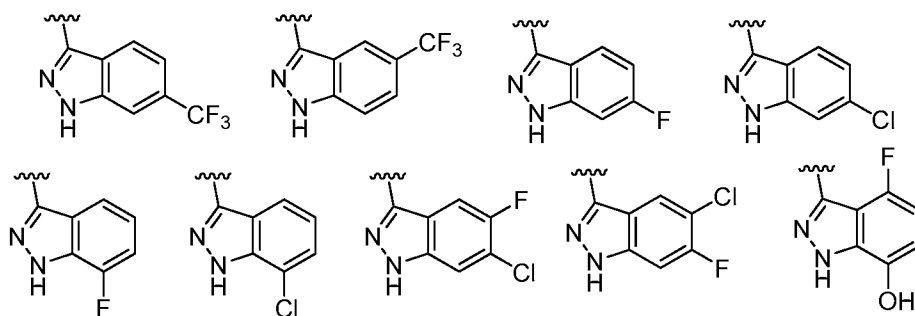


[00119] In certain embodiments, A<sup>2</sup> is . In certain other embodiments,



10 [00120] In certain embodiments, A<sup>2</sup> is one of the following:

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[00121] In certain embodiments,  $\text{R}^1$  is hydrogen. In certain embodiments,  $\text{R}^1$  is alkyl, such as methyl or ethyl. In certain embodiments,  $\text{R}^2$  is hydrogen. In certain embodiments,  $\text{R}^2$  is alkyl, such as methyl or ethyl. In certain embodiments,  $\text{R}^1$  and  $\text{R}^2$  are hydrogen.

- 5 [00122] In certain embodiments,  $\text{R}^3$  is halogen or haloalkyl. In certain embodiments,  $\text{R}^3$  is chloro or fluoro.

[00123] In certain embodiments,  $\text{R}^4$  represents independently for each occurrence hydrogen or methyl. In certain other embodiments,  $\text{R}^4$  is hydrogen.

[00124] In certain embodiments,  $\text{R}^5$  is hydrogen. In certain embodiments,  $\text{R}^5$  is methyl.

- 10 [00125] In certain embodiments,  $\text{R}^6$  is hydrogen. In certain embodiments,  $\text{R}^6$  is alkyl, such as methyl or ethyl. In certain embodiments,  $\text{R}^7$  is hydrogen. In certain embodiments,  $\text{R}^7$  is alkyl, such as methyl or ethyl. In certain embodiments,  $\text{R}^6$  and  $\text{R}^7$  are hydrogen.

[00126] In certain embodiments,  $\text{R}^4$  represents independently for each occurrence hydrogen or methyl,  $\text{R}^5$  is methyl, and  $\text{R}^6$  and  $\text{R}^7$  are hydrogen.

- 15 [00127] In certain embodiments,  $\text{R}^8$  is hydrogen.

[00128] In certain embodiments,  $\text{R}^9$  represents independently for each occurrence halogen or haloalkyl. In certain other embodiments,  $\text{R}^9$  represents independently for each occurrence chloro, fluoro, or trifluoromethyl.

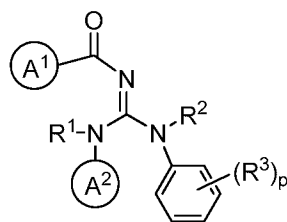
[00129] In certain embodiments,  $\text{R}^{10}$  is alkyl, such as methyl or ethyl.

- 20 [00130] In certain embodiments,  $m$  is 0. In certain other embodiments,  $m$  is 1.

[00131] In certain embodiments,  $n$  is 1 or 2. In certain embodiments,  $p$  is 1 or 2.

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[00132] Another aspect of the invention provides a family of compounds represented by Formula II-A:

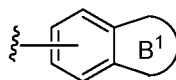


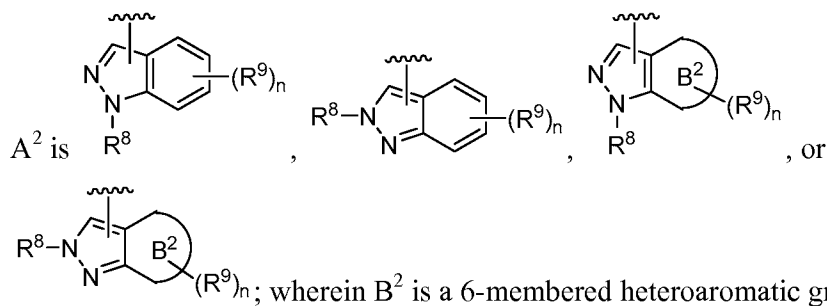
(II-A)

including all stereoisomers, geometric isomers, and tautomers; or a pharmaceutically acceptable salt or solvate of any of the foregoing; wherein:

A¹ is one of the following:

- (i) phenyl or a six-membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, cyano, -CO<sub>2</sub>R<sup>4</sup>, -C(O)R<sup>5</sup>, -S(O)R<sup>5</sup>, -SO<sub>2</sub>R<sup>5</sup>, -SO<sub>2</sub>N(R<sup>6</sup>)(R<sup>7</sup>), -C(O)N(R<sup>6</sup>)(R<sup>7</sup>), -N(R<sup>6</sup>)(R<sup>7</sup>), and -N(R<sup>4</sup>)C(O)(R<sup>5</sup>); or

- (ii)  that is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, and C<sub>1</sub>-C<sub>6</sub>alkoxy; wherein B¹ is a 5- or 6-membered heterocycle;



R¹ and R² each represent independently hydrogen or alkyl;

R³ represents independently for each occurrence halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyalkyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, or cyano;

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$R^4$  represents independently for each occurrence hydrogen, alkyl, or cycloalkyl; or two occurrences of  $R^4$  attached to the same carbon atom are taken together with said carbon atom to form a saturated carbocyclic ring;

$R^5$  represents independently for each occurrence alkyl or cycloalkyl;

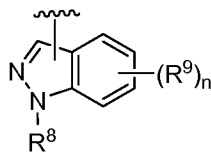
5  $R^6$  and  $R^7$  each represent independently for each occurrence hydrogen, alkyl, or cycloalkyl; or  $R^6$  and  $R^7$  are taken together with the nitrogen atom to which they are attached to form a 3 to 7 membered heterocyclic ring optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl, and  $C_1$ - $C_6$ alkoxy;

10  $R^8$  is hydrogen, or  $R^8$  is alkyl substituted by hydroxyl,  $-N(H)(R^6)$ , heterocycloalkyl,  $-N(H)C(O)R^{10}$ ,  $-C(O)N(H)(R^6)$ , or  $-N(H)C(O)N(R^6)(R^7)$ ;

$R^9$  represents independently for each occurrence halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl,  $C_1$ - $C_6$ alkoxy, or cyano;

$R^{10}$  is alkyl, cycloalkyl, aryl, or aralkyl; and

15 n and p each represent independently 0, 1, 2, or 3; and

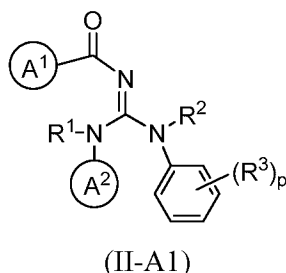


provided that if  $A^2$  is  $R^8$  and  $R^3$  is halogen or haloalkyl, then n is 1, 2 or 3.

[00133] Definitions of the variables in Formula II-A 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 which the variables are defined by (i) or (ii), e.g., such as where  $A^1$  is phenyl or a six-membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen and haloalkyl,  $R^1$  is hydrogen,  $R^2$  is hydrogen, and  $R^3$  is halogen. Further embodiments described above for Formula II, such as the definitions of variables associated with Formula II, are reiterated here for use in connection with Formula II-A.

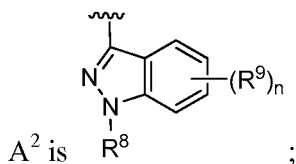
- 35 -

[00134] Another aspect of the invention provides a family of compounds represented by Formula II-A1:



5 including all stereoisomers, geometric isomers, and tautomers; or a pharmaceutically acceptable salt or solvate of any of the foregoing; wherein:

A<sup>1</sup> is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, and hydroxyl;



10 R<sup>1</sup> and R<sup>2</sup> are hydrogen;

R<sup>3</sup> represents independently for each occurrence halogen or haloalkyl;

R<sup>8</sup> is hydrogen;

R<sup>9</sup> represents independently for each occurrence halogen, haloalkyl, alkyl, hydroxyl, or C<sub>1</sub>-C<sub>6</sub>alkoxy;

15 n is 1 or 2; and

p is 1, 2, or 3.

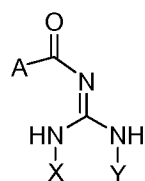
[00135] Definitions of the variables in Formula II-A1 above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition is a collection 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 which the variables are defined by (i) or (ii), e.g., such as where A<sup>1</sup> is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen and haloalkyl, and R<sup>3</sup> is halogen.

[00136] The description above for Formula I, I-A, I-A1, II, II-A, and II-A1 describes multiple embodiments providing definitions for variables used herein. The application specifically contemplates all combinations of such embodiments.

[00137] In certain embodiments, the compound is one of the compounds listed in any one of Tables 1-4 herein, or a pharmaceutically acceptable salt thereof. It is understood that the foregoing compounds can be combined with a pharmaceutically acceptable carrier to produce a pharmaceutical composition.

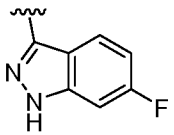
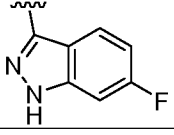
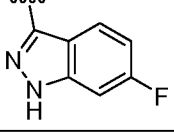
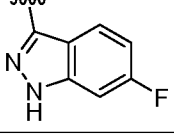
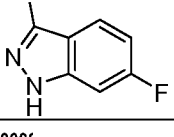
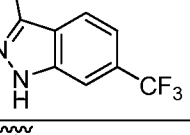
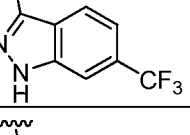
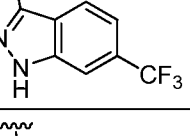
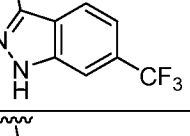
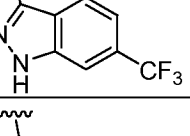
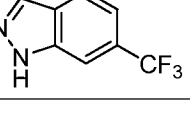
5

TABLE 1

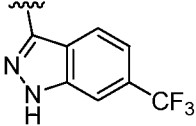
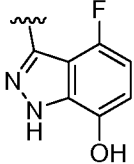
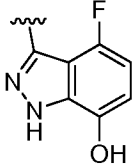
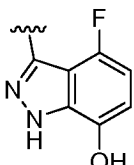
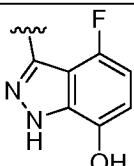
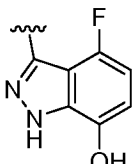
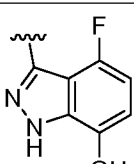
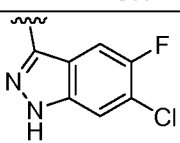
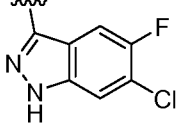


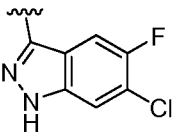
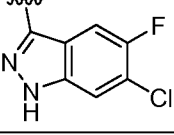
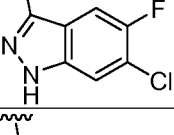
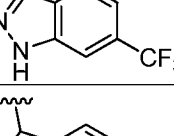
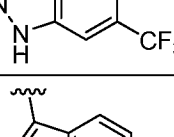
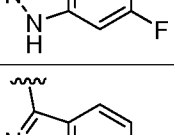
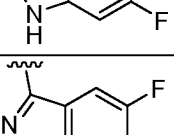
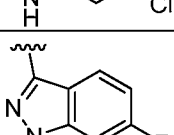
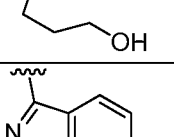
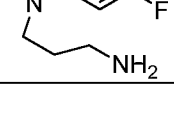
| No. | A                       | X | Y                            |
|-----|-------------------------|---|------------------------------|
| I-1 | 3-chlorophenyl          |   | isobutyl                     |
| I-2 | 4-chlorophenyl          |   | sec-butyl                    |
| I-3 | 3-fluorophenyl          |   | tert-butyl                   |
| I-4 | 4-fluorophenyl          |   | ethyl                        |
| I-5 | 3,4-dichlorophenyl      |   | propyl                       |
| I-6 | 3,4-difluorophenyl      |   | isopropyl                    |
| I-7 | 4-trifluoromethylphenyl |   | -C(H)(Me)CH <sub>2</sub> OMe |

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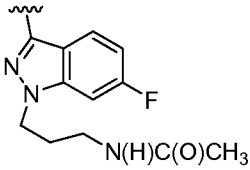
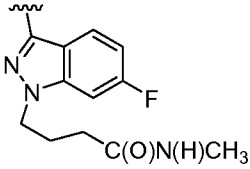
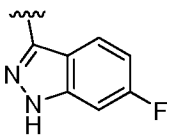
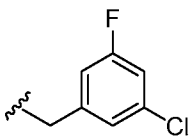
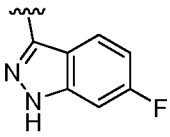
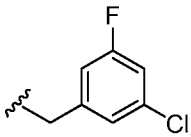
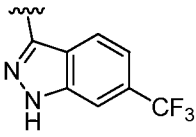
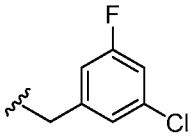
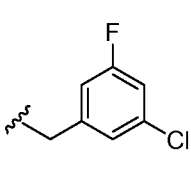
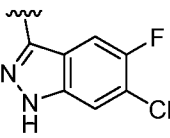
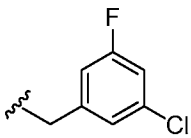
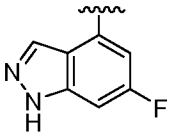
| No.  | A                       | X                                                                                   | Y                                    |
|------|-------------------------|-------------------------------------------------------------------------------------|--------------------------------------|
| I-8  | 3-chlorophenyl          |    | -CH <sub>2</sub> CH <sub>2</sub> OMe |
| I-9  | 4-chlorophenyl          |    | -CH <sub>2</sub> CH <sub>2</sub> OEt |
| I-10 | 3-fluorophenyl          |    | cyclopropyl                          |
| I-11 | 4-fluorophenyl          |    | cyclopentyl                          |
| I-12 | 3,4-dichlorophenyl      |   | cyclohexyl                           |
| I-13 | 3,4-difluorophenyl      |  | 1-methylcyclobutyl                   |
| I-14 | 4-trifluoromethylphenyl |  | 1-methylcyclopentyl                  |
| I-15 | 3-chlorophenyl          |  | 4-methylcyclohexyl                   |
| I-16 | 4-chlorophenyl          |  | isobutyl                             |
| I-17 | 3-fluorophenyl          |  | sec-butyl                            |
| I-18 | 4-fluorophenyl          |  | <i>tert</i> -butyl                   |

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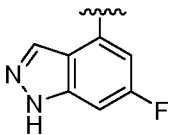
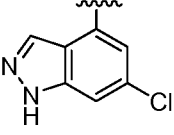
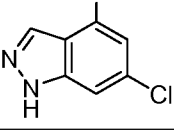
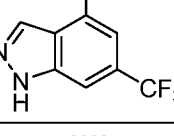
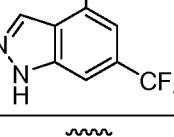
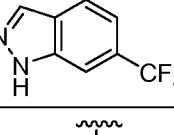
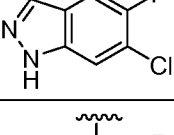
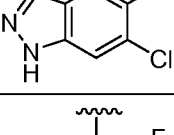
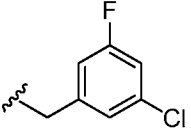
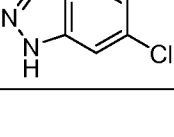
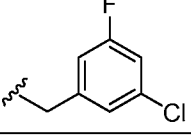
| No.  | A                       | X                                                                                   | Y                                    |
|------|-------------------------|-------------------------------------------------------------------------------------|--------------------------------------|
| I-19 | 3,4-dichlorophenyl      |    | ethyl                                |
| I-20 | 3,4-difluorophenyl      |    | propyl                               |
| I-21 | 4-trifluoromethylphenyl |    | isopropyl                            |
| I-22 | 3-chlorophenyl          |   | -C(H)(Me)CH <sub>2</sub> OMe         |
| I-23 | 4-chlorophenyl          |  | -CH <sub>2</sub> CH <sub>2</sub> OMe |
| I-24 | 3-fluorophenyl          |  | -CH <sub>2</sub> CH <sub>2</sub> OEt |
| I-25 | 4-fluorophenyl          |  | cyclopropyl                          |
| I-26 | 3,4-dichlorophenyl      |  | cyclopentyl                          |
| I-27 | 3,4-difluorophenyl      |  | cyclohexyl                           |

| No.  | A                       | X                                                                                   | Y                            |
|------|-------------------------|-------------------------------------------------------------------------------------|------------------------------|
| I-28 | 4-trifluoromethylphenyl |    | 1-methylcyclobutyl           |
| I-29 | 3-chlorophenyl          |    | 1-methylcyclopentyl          |
| I-30 | 4-chlorophenyl          |    | 4-methylcyclohexyl           |
| I-31 | 4-hydroxyphenyl         |   | isobutyl                     |
| I-32 | 4-hydroxyphenyl         |  | sec-butyl                    |
| I-33 | 4-hydroxyphenyl         |  | isopropyl                    |
| I-34 | 4-hydroxyphenyl         |  | -C(H)(Me)CH <sub>2</sub> OMe |
| I-35 | 4-hydroxyphenyl         |  | -C(H)(Me)CH <sub>2</sub> OMe |
| I-36 | 3-chlorophenyl          |  | isobutyl                     |
| I-37 | 4-chlorophenyl          |  | sec-butyl                    |

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| No.  | A                  | X                                                                                   | Y                                                                                     |
|------|--------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| I-38 | 3-fluorophenyl     |   | <i>tert</i> -butyl                                                                    |
| I-39 | 4-fluorophenyl     |   | isopropyl                                                                             |
| I-40 | 3-chlorophenyl     |    | -C(H)(Me)CH <sub>2</sub> OMe                                                          |
| I-41 | 3-fluorophenyl     |   |   |
| I-42 | 4-fluorophenyl     |  |  |
| I-43 | 3,4-dichlorophenyl |  |  |
| I-44 | 3,4-difluorophenyl |  |  |
| I-45 | 3,4-difluorophenyl |  |  |
| I-46 | 3-fluorophenyl     |  | isobutyl                                                                              |

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| No.  | A                       | X                                                                                   | Y                                                                                     |
|------|-------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| I-47 | 4-fluorophenyl          |    | sec-butyl                                                                             |
| I-48 | 3,4-dichlorophenyl      |    | isopropyl                                                                             |
| I-49 | 3,4-difluorophenyl      |    | -C(H)(Me)CH <sub>2</sub> OMe                                                          |
| I-50 | 4-trifluoromethylphenyl |   | -C(H)(Me)CH <sub>2</sub> OMe                                                          |
| I-51 | 3-chlorophenyl          |  | isobutyl                                                                              |
| I-52 | 4-chlorophenyl          |  | 1-methylcyclopentyl                                                                   |
| I-53 | 3-fluorophenyl          |  | cyclohexyl                                                                            |
| I-54 | 4-hydroxyphenyl         |  |  |
| I-55 | 4-hydroxyphenyl         |  |  |

### Prodrug Guanidine Compounds

[00138] Another aspect of the invention provides prodrugs of compounds described herein. Prodrugs are compounds that are transformed *in vivo* to yield a compound of Formula I, I-A, I-  
 5 A1, II, II-A, II-A1, a compound in Table 1, or compounds **1**, **2**, **3**, **4**, or A-1 through A-113 in

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Table 4, or a pharmaceutically acceptable salt, solvate of any of the foregoing. The transformation may occur by various mechanisms, such as through hydrolysis in blood. For example, if a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester  
 5 formed by the replacement of the hydrogen atom of the acid group with a group such as (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>2</sub>-C<sub>12</sub>)alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8  
 10 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C<sub>1</sub>-C<sub>2</sub>)alkylamino(C<sub>2</sub>-C<sub>3</sub>)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C<sub>1</sub>-C<sub>2</sub>)alkyl, N,N-di(C<sub>1</sub>-C<sub>2</sub>)alkylcarbamoyl-(C<sub>1</sub>-C<sub>2</sub>)alkyl and piperidino-, pyrrolidino- or morpholino(C<sub>2</sub>-C<sub>3</sub>)alkyl.

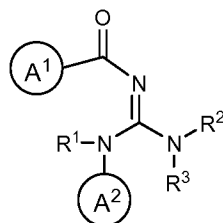
15 **[00139]** Similarly, if a compound of Formula (I) contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as (C<sub>1</sub>-C<sub>6</sub>)alkanoyloxymethyl, 1-((C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy)ethyl, 1-methyl-1-((C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy)ethyl (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyloxymethyl, N-(C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonylaminomethyl, succinoyl, (C<sub>1</sub>-C<sub>6</sub>)alkanoyl, α-amino(C<sub>1</sub>-C<sub>4</sub>)alkanoyl,  
 20 arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, P(O)(OH)<sub>2</sub>, -P(O)(O(C<sub>1</sub>-C<sub>6</sub>)alkyl)<sub>2</sub> or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

**[00140]** If a compound of Formula (I) incorporates an amine functional group, a prodrug can  
 25 be formed by the replacement of a hydrogen atom in the amine group with a group such as R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (C<sub>1</sub>-C<sub>10</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl or natural α-aminoacyl-natural α-aminoacyl, —C(OH)C(O)OY<sup>1</sup> wherein Y<sup>1</sup> is H, (C<sub>1</sub>-C<sub>6</sub>)alkyl or benzyl, -C(OY<sup>2</sup>)Y<sup>3</sup> wherein Y<sup>2</sup> is (C<sub>1</sub>-C<sub>4</sub>) alkyl and Y<sup>3</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkyl, carboxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, amino(C<sub>1</sub>-  
 30 C<sub>4</sub>)alkyl or mono-N— or di-N,N—(C<sub>1</sub>-C<sub>6</sub>)alkylaminoalkyl, —C(Y<sup>4</sup>)Y<sup>5</sup> wherein Y<sup>4</sup> is H or

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methyl and Y<sup>5</sup> is mono-N— or di-N,N—(C<sub>1</sub>-C<sub>6</sub>)alkylamino, morpholino, piperidin-1-yl or pyrrolidin-1-yl.

**[00141]** In certain embodiments, the prodrug compound is a compound represented by Formula III:

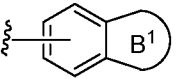


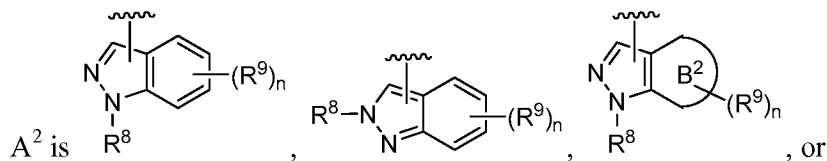
(III)

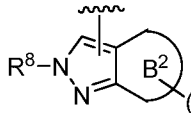
including all stereoisomers, geometric isomers, and tautomers; or a pharmaceutically acceptable salt or solvate of any of the foregoing; wherein:

A<sup>1</sup> is one of the following:

- 10 (i) phenyl or a six-membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, cyano, -CO<sub>2</sub>R<sup>4</sup>, -C(O)R<sup>5</sup>, -S(O)R<sup>5</sup>, -SO<sub>2</sub>R<sup>5</sup>, -SO<sub>2</sub>N(R<sup>6</sup>)(R<sup>7</sup>), -C(O)N(R<sup>6</sup>)(R<sup>7</sup>), -N(R<sup>6</sup>)(R<sup>7</sup>), and -N(R<sup>4</sup>)C(O)(R<sup>5</sup>); or

- 15 (ii)  that is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, and C<sub>1</sub>-C<sub>6</sub>alkoxy; wherein B<sup>1</sup> is a 5-membered or 6-membered heterocycle;



- 20 ; wherein B<sup>2</sup> is a 6-membered heteroaromatic group;

R<sup>1</sup> and R<sup>2</sup> each represent independently hydrogen or alkyl;

R<sup>3</sup> is one of the following:

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- (i) alkyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of hydroxyl, alkoxy,  $-O-(C(R^4)_2)_m$ -alkoxy,  $-O-(C(R^4)_2)_m-OH$ ,  $-N(R^6)(R^7)$ , cycloalkyl, heterocycloalkyl,  $-N(R^6)C(O)R^8$ ,  $-C(O)N(R^6)(R^7)$ ,  $-N(R^6)C(O)N(R^6)(R^7)$ , halogen, haloalkyl, and cyano; or
- 5 (ii) cycloalkyl or heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl, hydroxyalkyl, alkoxy,  $-O-(C(R^4)_2)_m$ -alkoxy,  $-O-(C(R^4)_2)_m-OH$ , and cyano;

$R^4$  represents independently for each occurrence hydrogen, alkyl, or cycloalkyl; or two  
10 occurrences of  $R^4$  attached to the same carbon atom are taken together with said carbon atom to form a saturated carbocyclic ring;

$R^5$  represents independently for each occurrence alkyl or cycloalkyl;

$R^6$  and  $R^7$  each represent independently for each occurrence hydrogen, alkyl, or cycloalkyl; or  $R^6$  and  $R^7$  are taken together with the nitrogen atom to which they are attached to  
15 form a 3 to 7 membered heterocyclic ring optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl, and  $C_1-C_6$ alkoxy;

$R^8$  is alkyl (such as methyl),  $-CH_2-S$ -alkyl,  $-CO_2$ -alkylene-Z,  $-CO_2$ -alkyl, or  $-C(O)$ -alkyl optionally substituted by one or more of hydroxyl, halogen, and  $-N(R^6)(R^7)$ ;

20  $R^9$  represents independently for each occurrence halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl,  $C_1-C_6$ alkoxy, or cyano;

Z is  $-O-P(O)(OH)_2$ ,  $-OC(O)$ -arylene-alkylene- $O-P(O)(OH)_2$ ,  $-OC(O)$ -arylene- $O-P(O)(OH)_2$ , or  $-OC(O)$ -alkylene- $O-P(O)(OH)_2$ ;

n is 0, 1, 2, 3, or 4; and

25 m is 1, 2, 3, 4, or 5.

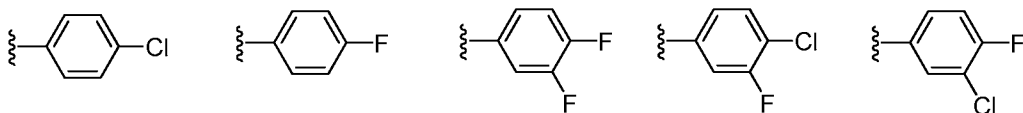
**[00142]** It is understood that upon administration of a compound of Formula III to a patient, the group defined by variable  $R^8$  of Formula III is removed *in vivo* to provide a compound with biological activity (e.g., inhibition of ATPase activity). Removal of the group defined by variable  $R^8$  of Formula III produces a compound where variable  $R^8$  is hydrogen.

30 **[00143]** Definitions of the variables in Formula III 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

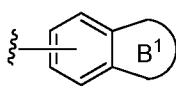
- 45 -

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 which the variables are defined by (i) or (ii), e.g., such as where  $A^1$  is phenyl or a six-membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen and haloalkyl,  $R^1$  is hydrogen,  $R^2$  is hydrogen,  $R^3$  is alkyl, and  $n$  is 1 or 2.

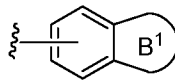
**[00144]** In certain embodiments,  $A^1$  is phenyl or a six-membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, and  $C_1$ - $C_6$ alkoxy. In certain other embodiments,  $A^1$  is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, and hydroxyl. In certain other embodiments,  $A^1$  is phenyl substituted with 1 or 2 substituents independently selected from the group consisting of chloro, fluoro, and trifluoromethyl. In certain other embodiments,  $A^1$  is phenyl substituted with 1 or 2 substituents independently selected from the group consisting of chloro and fluoro. In certain other embodiments,  $A^1$  is one of the following:

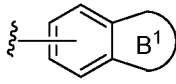


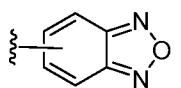
**[00145]** In certain embodiments,  $A^1$  is a six-membered heteroaryl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, and heterocycloalkyl. In certain other embodiments,  $A^1$  is a six-membered heteroaryl substituted with by heterocycloalkyl. In certain other embodiments,  $A^1$  is pyridinyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, and heterocycloalkyl. In certain other embodiments,  $A^1$  is a pyridinyl substituted with a 6-membered heterocycloalkyl. In certain embodiments,  $A^1$  is a pyridinyl substituted with morpholinyl.

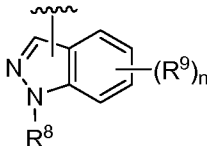
**[00146]** In certain other embodiments,  $A^1$  is  optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, and  $C_1$ - $C_6$ alkoxy; wherein  $B^1$  is a 5-membered or 6-

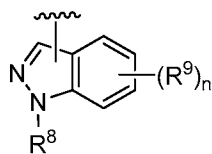
- 46 -

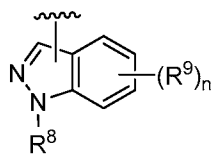
membered heterocycle. In certain other embodiments, A<sup>1</sup> is  optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, and C<sub>1</sub>-C<sub>6</sub>alkoxy; wherein B<sup>1</sup>

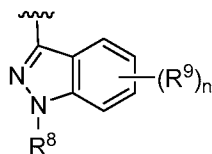
is a 5-membered heteroaromatic group. In certain other embodiments, A<sup>1</sup> is  wherein B<sup>1</sup> is a 5-membered heteroaromatic group. In certain other embodiments, A<sup>1</sup> is



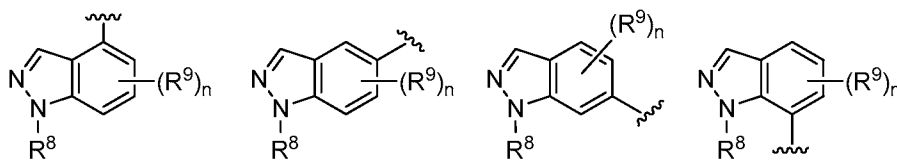
[00147] In certain embodiments, A<sup>2</sup> is . It is understood that the chemical



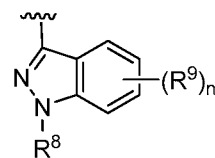
formula  conveys that the indazolyl structure shown can be attached to the guanidine core via (i) a carbon atom of the 5-membered ring of the indazolyl structure or (ii) a carbon atom of the 6-membered ring of the indazolyl structure. An example of where the indazolyl is attached to the guanidine core via a carbon atom of the 5-membered ring of the indazolyl structure is depicted below:

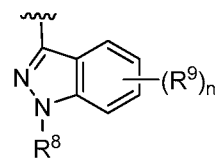


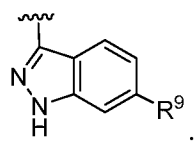
[00148] Examples of where the indazolyl is attached to the guanidine core via a carbon atom of the 6-membered ring of the indazolyl structure is depicted by the following formulae:

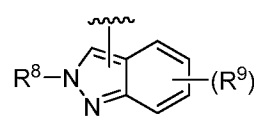


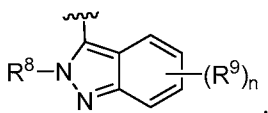
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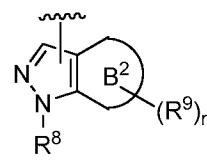


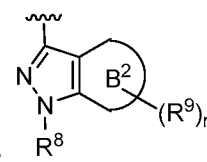
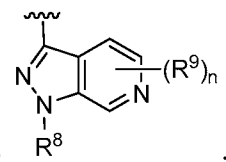
[00149] Accordingly, in certain other embodiments,  $A^2$  is . In certain

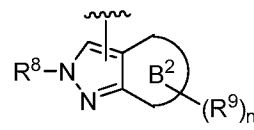
embodiments,  $A^2$  is .

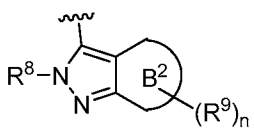
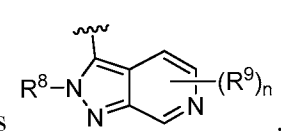
[00150] In certain embodiments,  $A^2$  is . In certain other embodiments,

$A^2$  is .

5 [00151] In certain embodiments,  $A^2$  is . In certain other embodiments,  $A^2$

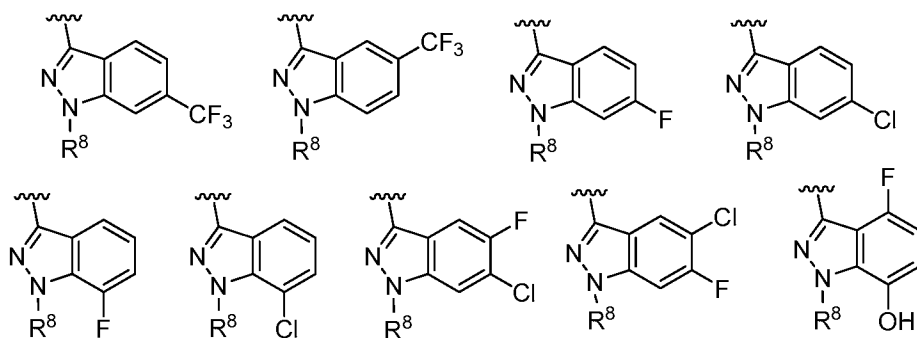
is . In certain other embodiments,  $A^2$  is .

[00152] In certain embodiments,  $A^2$  is . In certain other embodiments,

$A^2$  is . In certain other embodiments,  $A^2$  is .

[00153] In certain embodiments,  $A^2$  is one of the following:

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**[00154]** In certain embodiments,  $R^1$  is hydrogen. In certain embodiments,  $R^1$  is alkyl, such as methyl or ethyl. In certain embodiments,  $R^2$  is hydrogen. In certain embodiments,  $R^2$  is alkyl, such as methyl or ethyl. In certain embodiments,  $R^1$  and  $R^2$  are hydrogen.

- 5 **[00155]** In certain embodiments,  $R^3$  is alkyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of hydroxyl, alkoxy,  $-O-(C(R^4)_2)_m$ -alkoxy,  $-O-(C(R^4)_2)_m$ -OH,  $-N(R^6)(R^7)$ , and cycloalkyl. In certain other embodiments,  $R^3$  is alkyl or cycloalkyl. In certain other embodiments,  $R^3$  is cyclobutyl, cyclopentyl, cyclohexyl, or  $C_{2-6}$  alkyl. In certain other embodiments,  $R^3$  is  $C_{1-6}$  alkyl substituted by  $C_{1-6}$  alkoxy. In certain other embodiments,  $R^3$  is alkyl, such as propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, or 2,2-dimethyl-1-propyl.

- 15 **[00156]** In certain embodiments,  $R^3$  is cycloalkyl or heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, and alkyl. In certain other embodiments,  $R^3$  is cycloalkyl substituted by alkyl. In certain other embodiments,  $R^3$  is  $C_{3-6}$  cycloalkyl substituted by  $C_{1-6}$  alkyl. In certain other embodiments,  $R^3$  is heterocycloalkyl, such as morpholinyl.

**[00157]** In certain embodiments,  $R^4$  represents independently for each occurrence hydrogen or methyl. In certain other embodiments,  $R^4$  is hydrogen.

- 20 **[00158]** In certain embodiments,  $R^5$  is hydrogen. In certain embodiments,  $R^5$  is methyl.

**[00159]** In certain embodiments,  $R^6$  is hydrogen. In certain embodiments,  $R^6$  is alkyl, such as methyl or ethyl. In certain embodiments,  $R^7$  is hydrogen. In certain embodiments,  $R^7$  is alkyl, such as methyl or ethyl. In certain embodiments,  $R^6$  and  $R^7$  are hydrogen.

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[00160] In certain embodiments,  $R^8$  is  $-CO_2$ -alkylene-Z. In certain embodiments, Z is  $-O-P(O)(OH)_2$ .

[00161] In certain embodiments,  $R^9$  represents independently for each occurrence halogen or haloalkyl. In certain other embodiments,  $R^9$  represents independently for each occurrence  
5 chloro, fluoro, or trifluoromethyl.

[00162] In certain embodiments, m is 1 or 2.

[00163] In certain embodiments, n is 1 or 2.

[00164] In certain embodiments, the compound of Formula III is one of the following:  
compound 5, 6, 7, or 8 from Examples 9-12 or compound A-114, A-115, or A-116 from Table  
10 2.

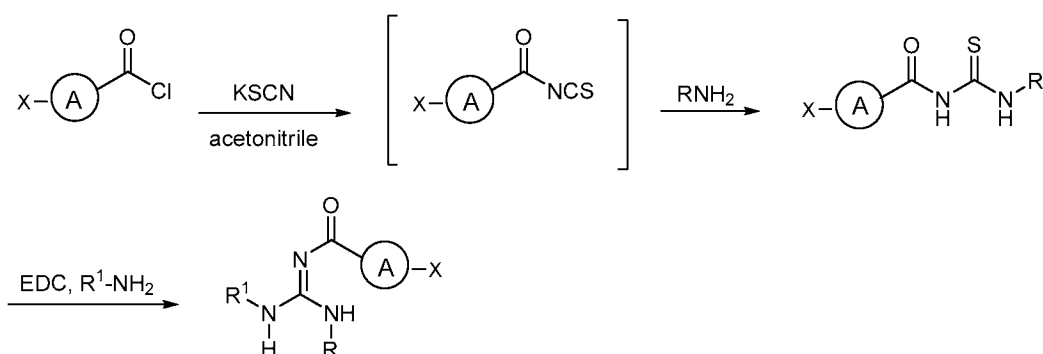
Exemplary Synthetic Procedures for Making Guanidine Compounds

[00165] Exemplary methods for preparing compounds described herein are provided in the examples. Further exemplary procedures for making various compounds described herein are described in Scheme 1 below. The synthetic scheme is provided for the purpose of illustrating  
15 the invention, but not for limiting the scope or spirit of the invention. Starting materials can be obtained from commercial sources or be prepared based on procedures described in the literature.

[00166] The synthetic route in Scheme 1 involves reacting an optionally substituted acyl chloride with potassium thiocyanate to form an acyl isothiocyanate intermediate. This acyl  
20 isothiocyanate intermediate is treated with an amino-indazole ( $RNH_2$ ) to form an acyl thiourea. The acyl thiourea is reacted with 1-ethyl-2',2'-dimethylaminopropylcarbodiimide (EDC) and a second amine compound (e.g.,  $R^1-NH_2$ ) to form the desired indazole guanidine compound. To the extent either the amino-indazole or the second amine compound contain a further functional group that may undergo reaction under the conditions illustrated in Scheme 1, standard  
25 protecting group strategies for protection and deprotection may be employed. See, for example, Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 2<sup>nd</sup> ed.; Wiley: New York, 1991.

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SCHEME 1



where  $A$  is phenyl or a 6-membered heteroaryl group and  $X$  is hydrogen or a substituent. It is understood, for example, that group  $A$  may be contain multiple substituents (i.e., multiple  $X$  groups).

### III. Therapeutic Applications of Indazole Guanidine Compounds

**[00167]** It is contemplated that the guanidine compounds described herein, such as the guanidine compounds of Formula I, I-A, I-A1, II, II-A, II-A1, or III, provide therapeutic benefits to patients suffering from any one or more of a number of conditions, *e.g.*, diseases characterized by dysregulation of  $F_1F_0$ -ATPase activity, diseases characterized by dysregulation of necrosis and/or apoptosis processes in a cell or tissue, disease characterized by aberrant cell growth and/or hyperproliferation. The compounds described herein can also be used to treat a variety of dysregulatory disorders related to cellular death as described elsewhere herein. Additionally, the compounds described herein can be used to inhibit ATP synthesis.

**[00168]** Accordingly, one 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 indazole guanidine compounds described herein, *e.g.*, a compound of Formula I, I-A, I-A1, II, II-A, II-A1, or III, as described in Section II above, in order to ameliorate a symptom of the disorder.

**[00169]** A large number of medical disorders can be treated using the guanidine compounds described herein. For example, the compounds described herein can be used to treat medical disorders characterized by dysregulation of necrosis and/or apoptosis processes in a cell or tissue, diseases characterized by aberrant cell growth and/or hyperproliferation, *etc.*, or lupus,

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rheumatoid arthritis, psoriasis, chronic graft-versus-host disease, acute graft-versus-host disease, Crohn's disease, inflammatory bowel disease, multiple sclerosis, cardiovascular disease, myeloma, lymphoma, cancer, and bacterial infection. In certain embodiments, the cancer is a solid tumor, leukemia, colon cancer, pancreatic cancer, breast cancer, ovarian  
5 cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, lung cancer, small cell lung cancer, non-small cell lung cancer, bladder cancer, stomach cancer, cervical cancer, testicular tumor, skin cancer, rectal cancer, thyroid cancer, kidney cancer, uterus cancer, esophagus cancer, liver cancer, an acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, or  
10 retinoblastoma.

**[00170]** Although not wishing to be bound to a particular theory, it is believed that the compounds impart therapeutic benefit by modulating (*e.g.*, inhibiting) the activity of the  $F_1F_0$ -ATPase complexes (*e.g.*, mitochondrial  $F_1F_0$ -ATPase complexes) in affected cells or tissues. In some embodiments, the compositions of the present invention are used to treat immune/chronic  
15 inflammatory conditions (*e.g.*, psoriasis, autoimmune disorders, organ-transplant rejection, and epidermal hyperplasia). In further embodiments, the compositions of the present invention are used in conjunction with stenosis therapy to treat compromised (*e.g.*, occluded) vessels.

**[00171]** In certain embodiments, a composition comprising a guanidine compound is administered under conditions (*e.g.*, timing, dose, co-administration with other agent, mode of  
20 administration, selection of subject, use of targeting agents, etc.) that maximize desired effects directed at the  $F_1F_0$ -ATPase.

**[00172]** In certain embodiments, the medical disorder is an immune disorder. In certain other embodiments, the medical disorder is an inflammatory disorder. In certain other embodiments, the medical disorder is an autoimmune disorder. In certain other embodiments,  
25 the medical 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 Sprue, idiopathic thrombocytopenic thrombotic purpura, myasthenia gravis, Sjogren's syndrome, scleroderma, ulcerative colitis, asthma, uveitis, or epidermal hyperplasia.

**[00173]** In certain other embodiments, the medical disorder is cartilage inflammation, bone degradation, arthritis, juvenile arthritis, juvenile rheumatoid arthritis, pauciarticular juvenile

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- 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, systemic onset rheumatoid arthritis, ankylosing spondylitis, enteropathic arthritis, reactive arthritis, Reter's Syndrome, dermatomyositis, psoriatic arthritis, vasculitis, myolitis, polymyolitis, dermatomyolitis, osteoarthritis, polyarteritis nodossa, Wegener's granulomatosis, arteritis, polymyalgia rheumatica, sarcoidosis, sclerosis, primary biliary sclerosis, sclerosing cholangitis, dermatitis, atopic dermatitis, atherosclerosis, Still's disease, chronic obstructive pulmonary disease, Guillain-Barre disease, Type I diabetes mellitus, Graves' disease, Addison's disease, Raynaud's phenomenon, or autoimmune hepatitis. In certain embodiments, the psoriasis is plaque psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, or erythrodermic psoriasis.
- 15 **[00174]** In certain other embodiments, the medical disorder is Crohn's disease, inflammatory bowel disease, multiple sclerosis, graft-versus-host disease, lupus, rheumatoid arthritis, or psoriasis. In certain other embodiments, the medical disorder is cardiovascular disease, myeloma, lymphoma, or cancer. In certain other embodiments, the medical disorder is lupus, rheumatoid arthritis, psoriasis, graft-versus-host disease, myeloma, or lymphoma. In certain
- 20 other embodiments, the medical disorder is cardiovascular disease or cancer. In certain other embodiments, the medical disorder is Crohn's disease, inflammatory bowel disease, or multiple sclerosis. In certain other embodiments, the medical disorder is graft-versus-host disease. In further embodiments, the medical disorder is a bacterial infection. In certain embodiments, the patient (or subject) is a human.
- 25 **[00175]** As indicated above, the guanidine compounds described herein can be used in the treatment of a bacterial infection. A variety of bacteria are contemplated to be susceptible to the guanidine compounds. Representative bacteria include *Staphylococci* species, e.g., *S. aureus*; *Enterococci* species, e.g., *E. faecalis* and *E. faecium*; *Streptococci* species, e.g., *S. pyogenes* and *S. pneumoniae*; *Escherichia* species, e.g., *E. coli*, including enterotoxigenic, enteropathogenic, enteroinvasive, enterohemorrhagic and enteroaggregative *E. coli* strains; *Haemophilus* species, e.g., *H. influenza*; and *Moraxella* species, e.g., *M. catarrhalis*. Other
- 30 examples include *Mycobacteria* species, e.g., *M. tuberculosis*, *M. avian-intracellulare*, *M.*

*kansasii*, *M. bovis*, *M. africanum*, *M. genavense*, *M. leprae*, *M. xenopi*, *M. simiae*, *M. scrofulaceum*, *M. malmoense*, *M. celatum*, *M. abscessus*, *M. chelonae*, *M. szulgai*, *M. gordonae*, *M. haemophilum*, *M. fortuni* and *M. marinum*; *Corynebacteria* species, e.g., *C. diphtheriae*; *Vibrio* species, e.g., *V. cholerae*; *Campylobacter* species, e.g., *C. jejuni*;

5 *Helicobacter* species, e.g., *H. pylori*; *Pseudomonas* species, e.g., *P. aeruginosa*; *Legionella* species, e.g., *L. pneumophila*; *Treponema* species, e.g., *T. pallidum*; *Borrelia* species, e.g., *B. burgdorferi*; *Listeria* species, e.g., *L. monocytogenes*; *Bacillus* species, e.g., *B. cereus*; *Bordetella* species, e.g., *B. pertussis*; *Clostridium* species, e.g., *C. perfringens*, *C. tetani*, *C. difficile* and *C. botulinum*; *Neisseria* species, e.g., *N. meningitidis* and *N. gonorrhoeae*;

10 *Chlamydia* species, e.g., *C. psittaci*, *C. pneumoniae* and *C. trachomatis*; *Rickettsia* species, e.g., *R. rickettsii* and *R. prowazekii*; *Shigella* species, e.g., *S. sonnei*; *Salmonella* species, e.g., *S. typhimurium*; *Yersinia* species, e.g., *Y. enterocolitica* and *Y. pseudotuberculosis*; *Klebsiella* species, e.g., *K. pneumoniae*; *Mycoplasma* species, e.g., *M. pneumoniae*; and *Trypanosoma brucei*. In certain embodiments, the guanidine compounds described herein are used to treat a

15 subject suffering from a bacterial infection selected from the group consisting of *S. aureus*, *E. faecalis*, *E. faecium*, *S. pyogenes*, *S. pneumoniae*, and *P. aeruginosa*. In certain embodiments, the guanidine compounds described herein are used to treat a subject suffering from a *Trypanosoma brucei* infection.

[00176] The antibacterial activity of the compounds described herein may be evaluated

20 using standard assays known in the art, such as the microbroth dilution minimum inhibition concentration (MIC) assay, as further described in National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Susceptibility Testing; Fourteenth Informational Supplement. NCCLS document M100-S14 {ISBN 1-56238-516-X}. This assay may be used to determine the minimum concentration of a compound necessary to prevent

25 visible bacterial growth in a solution. In general, the drug to be tested is serially diluted into wells, and aliquots of liquid bacterial culture are added. This mixture is incubated under appropriate conditions, and then tested for growth of the bacteria. Compounds with low or no antibiotic activity (a high MIC) will allow growth at high concentrations of compound, while compounds with high antibiotic activity will allow bacterial growth only at lower

30 concentrations (a low MIC).

[00177] The assay uses stock bacterial culture conditions appropriate for the chosen strain of bacteria. Stock cultures from the permanent stock culture collection can be stored as frozen

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suspensions at -70°C. Cultures may be suspended in 10% skim milk (BD) prior to snap freezing in dry ice/ethanol and then placed in a -70°C freezer. Cultures may be maintained on Tryptic Soy Agar containing 5% Sheep Blood at room temperature (20°C), and each culture may be recovered from frozen form and transferred an additional time before MIC testing.

- 5 Fresh plates are inoculated the day before testing, incubated overnight, and checked to confirm purity and identity.

[00178] The identity and purity of the cultures recovered from the stock culture can be confirmed to rule out the possibility of contamination. The identity of the strains may be confirmed by standard microbiological methods (See, e.g., Murray *et al.*, Manual of Clinical Microbiology, Eighth Edition. ASM Press {ISBN 1-55581-255-4}). In general, cultures are streaked onto appropriate agar plates for visualization of purity, expected colony morphology, and hemolytic patterns. Gram stains can also be utilized. The identities are confirmed using a MicroScan WalkAway 40 SI Instrument (Dade Behring, West Sacramento, California). This device utilizes an automated incubator, reader, and computer to assess for identification purposes the biochemical reactions carried out by each organism. The MicroScan WalkAway can also be used to determine a preliminary MIC, which may be confirmed using the method described below.

[00179] Frozen stock cultures may be used as the initial source of organisms for performing microbroth dilution minimum inhibition concentration (MIC) testing. Stock cultures are passed on their standard growth medium for at least 1 growth cycle (18-24 hours) prior to their use. Most bacteria may be prepared directly from agar plates in 10 mL aliquots of the appropriate broth medium. Bacterial cultures are adjusted to the opacity of a 0.5 McFarland Standard (optical density value of 0.28-0.33 on a Perkin-Elmer Lambda EZ150 Spectrophotometer, Wellesley, Massachusetts, set at a wavelength of 600nm). The adjusted cultures are then diluted 400 fold (0.25 mL inoculum + 100 mL broth) in growth media to produce a starting suspension of approximately  $5 \times 10^5$  colony forming units (CFU)/mL. Most bacterial strains may be tested in cation adjusted Mueller Hinton Broth (CAMHB).

[00180] Test compounds ("drugs") are solubilized in a solvent suitable for the assay, such as DMSO. Drug stock solutions may be prepared on the day of testing. Microbroth dilution stock plates may be prepared in two dilution series, 64 to 0.06 µg drug/mL and 0.25 to 0.00025 µg drug/mL. For the high concentration series, 200 µL of stock solution (2 mg/mL) is added to

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duplicate rows of a 96-well microtiter plate. This is used as the first well in the dilution series. Serial two-fold decremental dilutions are made using a BioMek FX robot (Beckman Coulter Inc., Fullerton, CA) with 10 of the remaining 11 wells, each of which will contain 100  $\mu$ L of the appropriate solvent/diluent. Row 12 contains solvent/diluent only and serves as the control.

- 5 For the first well of the low concentration series, 200  $\mu$ L of an 8  $\mu$ g/mL stock are added to duplicate rows of a 96-well plate. Serial two-fold dilutions are made as described above.

**[00181]** Daughter 96-well plates may be spotted (3.2  $\mu$ L/well) from the stock plates listed above using the BioMek FX robot and used immediately or frozen at -70°C until use. Aerobic organisms are inoculated (100  $\mu$ L volumes) into the thawed plates using the BioMek FX robot.

- 10 The inoculated plates are placed in stacks and covered with an empty plate. These plates are then incubated for 16 to 24 hours in ambient atmosphere according to CLSI guidelines (National Committee for Clinical Laboratory Standards, Methods for Dilution, Antimicrobial Tests for Bacteria that Grow Aerobically; Approved Standard-Sixth Edition. NCCLS document M7-A6 {ISBN 1-56238-486-4}).

- 15 **[00182]** After inoculation and incubation, the degree of bacterial growth can be estimated visually with the aid of a Test Reading Mirror (Dynex Technologies 220 16) in a darkened room with a single light shining directly through the top of the microbroth tray. The MIC is the lowest concentration of drug that prevents macroscopically visible growth under the conditions of the test.

- 20 **[00183]** Additionally, any one or more of the indazole guanidine compounds described herein can be used to treat a  $F_1F_0$ -ATP hydrolase associated disorder (e.g., myocardial infarction, ventricular hypertrophy, coronary artery disease, non-Q wave MI, congestive heart failure, cardiac arrhythmias, unstable angina, chronic stable angina, Prinzmetal's angina, high blood pressure, intermittent claudication, peripheral occlusive arterial disease, thrombotic or  
25 thromboembolic symptoms of thromboembolic stroke, venous thrombosis, arterial thrombosis, cerebral thrombosis, pulmonary embolism, cerebral embolism, thrombophilia, disseminated intravascular coagulation, restenosis, atrial fibrillation, ventricular enlargement, atherosclerotic vascular disease, atherosclerotic plaque rupture, atherosclerotic plaque formation, transplant atherosclerosis, vascular remodeling atherosclerosis, cancer, surgery, inflammation, systematic  
30 infection, artificial surfaces, interventional cardiology, immobility, medication, pregnancy and

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fetal loss, and diabetic complications comprising retinopathy, nephropathy and neuropathy) in a subject.

#### Combination Therapy

[00184] Additionally, the guanidine compounds described herein can be used in combination with at least one other therapeutic agent, such as potassium channel openers, calcium channel blockers, sodium hydrogen exchanger inhibitors, antiarrhythmic agents, antiatherosclerotic agents, anticoagulants, antithrombotic agents, prothrombolytic agents, fibrinogen antagonists, diuretics, antihypertensive agents, ATPase inhibitors, mineralocorticoid receptor antagonists, phosphodiesterase inhibitors, antidiabetic agents, anti-inflammatory agents, antioxidants, angiogenesis modulators, antiosteoporosis agents, hormone replacement therapies, hormone receptor modulators, oral contraceptives, antiobesity agents, antidepressants, antianxiety agents, antipsychotic agents, antiproliferative agents, antitumor agents, antiulcer and gastroesophageal reflux disease agents, growth hormone agents and/or growth hormone secretagogues, thyroid mimetics, anti-infective agents, antiviral agents, antibacterial agents, antifungal agents, cholesterol/lipid lowering agents and lipid profile therapies, and agents that mimic ischemic preconditioning and/or myocardial stunning, antiatherosclerotic agents, anticoagulants, antithrombotic agents, antihypertensive agents, antidiabetic agents, and antihypertensive agents selected from ACE inhibitors, AT-1 receptor antagonists, ET receptor antagonists, dual ET/AII receptor antagonists, vasopepsidase inhibitors, an antiplatelet agent selected from GPIIb/IIIa blockers, P2Y<sub>1</sub> and P2Y<sub>12</sub> antagonists, thromboxane receptor antagonists, or aspirin, along with a pharmaceutically-acceptable carrier or diluent in a pharmaceutical composition.

#### **IV. Pharmaceutical Compositions, Formulations, and Exemplary Administration Routes and Dosing Considerations**

[00185] Exemplary embodiments of various contemplated medicaments and pharmaceutical compositions are provided below.

##### **A. Preparing Medicaments**

[00186] Compounds of the present invention are useful in the preparation of medicaments to treat a variety of conditions, such as conditions associated with dysregulation of cell death, aberrant cell growth and hyperproliferation. One of skill in the art will appreciate that any one

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or more of the compounds described herein, including the many specific embodiments, are prepared by applying standard pharmaceutical manufacturing procedures. Such medicaments can be delivered to the subject by using delivery methods that are well-known in the pharmaceutical arts.

5           **B. Exemplary Pharmaceutical Compositions and Formulation**

[00187]   In some embodiments of the present invention, the compositions are administered alone, while in some other embodiments, the compositions are preferably present in a pharmaceutical formulation comprising at least one active ingredient/agent, as discussed above, together with a solid support or alternatively, together with one or more pharmaceutically acceptable carriers and optionally other therapeutic agents (*e.g.*, those described in section III hereinafter). Each carrier should be "acceptable" in the sense that it is compatible with the other ingredients of the formulation and not injurious to the subject.

[00188]   Contemplated formulations include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal, parenteral (including subcutaneous, intramuscular, intravenous and intradermal) and pulmonary administration. In some embodiments, formulations are conveniently presented in unit dosage form and are prepared by any method known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association (*e.g.*, mixing) the active ingredient with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

[00189]   Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets, wherein each preferably contains a predetermined amount of the active ingredient; as a powder or granules; as a solution or suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. In other embodiments, the active ingredient is presented as a bolus, electuary, or paste, *etc.*

[00190]   In some embodiments, tablets comprise at least one active ingredient and optionally one or more accessory agents/carriers are made by compressing or molding the respective agents. In some embodiments, compressed tablets are prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally

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mixed with a binder (*e.g.*, povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (*e.g.*, sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Molded tablets are made by molding in a suitable machine a mixture of the powdered compound (*e.g.*, active  
5 ingredient) moistened with an inert liquid diluent. Tablets may optionally be coated or scored and may 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. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

10 **[00191]** Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

15 **[00192]** Pharmaceutical compositions for topical administration according to the present invention are optionally formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils. In alternative embodiments, topical formulations comprise patches or dressings such as a bandage or adhesive plasters impregnated with active ingredient(s), and optionally one or more excipients or diluents. In some  
20 embodiments, the topical formulations include a compound(s) that enhances absorption or penetration of the active agent(s) through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide (DMSO) and related analogues.

**[00193]** If desired, the aqueous phase of a cream base includes, for example, at least about 30% w/w of a polyhydric alcohol, *i.e.*, an alcohol having two or more hydroxyl groups such as  
25 propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol and mixtures thereof.

**[00194]** In some embodiments, oily phase emulsions of this invention are constituted from known ingredients in a known manner. This phase typically comprises a lone emulsifier (otherwise known as an emulgent), it is also desirable in some embodiments for this phase to  
30 further comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil.

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[00195] Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier so as to act as a stabilizer. In some embodiments it is also preferable to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and/or fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

[00196] Emulgents and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate and sodium lauryl sulfate.

[00197] The choice of suitable oils or fats for the formulation is based on achieving the desired properties (*e.g.*, cosmetic properties), since the solubility of the active compound/agent in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus creams should preferably be non-greasy, non-staining and washable products with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

[00198] Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the agent.

[00199] Formulations for rectal administration may be presented as a suppository with suitable base comprising, for example, cocoa butter or a salicylate.

[00200] Formulations suitable for vaginal administration may be presented as pessaries, creams, gels, pastes, foams or spray formulations containing in addition to the agent, such carriers as are known in the art to be appropriate.

[00201] Formulations suitable for nasal administration, wherein the carrier is a solid, include coarse powders having a particle size, for example, in the range of about 20 to about 500 microns which are administered in the manner in which snuff is taken, *i.e.*, by rapid inhalation

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(e.g., forced) through the nasal passage from a container of the powder held close up to the nose. Other suitable formulations wherein the carrier is a liquid for administration include, but are not limited to, nasal sprays, drops, or aerosols by nebulizer, and include aqueous or oily solutions of the agents.

5 [00202] Formulations suitable for parenteral administration include aqueous and non-aqueous isotonic sterile injection solutions which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents, and liposomes or other microparticulate systems which are  
10 designed to target the compound to blood components or one or more organs. In some embodiments, the formulations are presented/formulated in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may  
15 be prepared from sterile powders, granules and tablets of the kind previously described.

[00203] Preferred unit dosage formulations are those containing a daily dose or unit, daily subdose, as herein above-recited, or an appropriate fraction thereof, of an agent.

[00204] It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art  
20 having regard to the type of formulation in question, for example, those suitable for oral administration may include such further agents as sweeteners, thickeners and flavoring agents. It also is intended that the agents, compositions and methods of this invention be combined with other suitable compositions and therapies. Still other formulations optionally include food additives (suitable sweeteners, flavorings, colorings, *etc.*), phytonutrients (e.g., flax seed oil),  
25 minerals (e.g., Ca, Fe, K, *etc.*), vitamins, and other acceptable compositions (e.g., conjugated linoelic acid), extenders, and stabilizers, *etc.*

### C. Exemplary Administration Routes and Dosing Considerations

[00205] Various delivery systems are known and can be used to administer therapeutic agents (e.g., exemplary compounds as described above) of the present invention, e.g.,  
30 encapsulation in liposomes, microparticles, microcapsules, receptor-mediated endocytosis, and the like. Methods of delivery include, but are not limited to, intra-arterial, intra-muscular,

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intravenous, intranasal, and oral routes. In specific embodiments, it may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, injection, or by means of a catheter.

5 [00206] The agents identified can be administered to subjects or individuals susceptible to or at risk of developing pathological growth of target cells and correlated conditions. When the agent is administered to a subject such as a mouse, a rat or a human patient, the agent can be added to a pharmaceutically acceptable carrier and systemically or topically administered to the subject. To identify patients that can be beneficially treated, a tissue sample is removed from  
10 the patient and the cells are assayed for sensitivity to the agent.

[00207] Therapeutic amounts are empirically determined and vary with the pathology being treated, the subject being treated and the efficacy and toxicity of the agent. When delivered to an animal, the method is useful to further confirm efficacy of the agent. One example of an animal model is MLR/MpJ-*lpr/lpr* ("MLR-*lpr*") (available from Jackson Laboratories, Bar  
15 Harbor, Maine ). MLR-*lpr* mice develop systemic autoimmune disease. Alternatively, other animal models can be developed by inducing tumor growth, for example, by subcutaneously inoculating nude mice with about  $10^5$  to about  $10^9$  hyperproliferative, cancer or target cells as defined herein. When the tumor is established, the compounds described herein are administered, for example, by subcutaneous injection around the tumor. Tumor measurements  
20 to determine reduction of tumor size are made in two dimensions using venier calipers twice a week. Other animal models may also be employed as appropriate. Such animal models for the above-described diseases and conditions are well-known in the art.

[00208] In some embodiments, *in vivo* administration is effected in one dose, continuously or intermittently throughout the course of treatment. Methods of determining the most  
25 effective means and dosage of administration are well known to those of skill in the art and vary with the composition used for therapy, the purpose of the therapy, the target cell being treated, and the subject being treated. Single or multiple administrations are carried out with the dose level and pattern being selected by the treating physician.

[00209] Suitable dosage formulations and methods of administering the agents are readily  
30 determined by those of skill in the art. Preferably, the 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

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more preferably at about 0.5 mg/kg to about 50 mg/kg. 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.

[00210] The pharmaceutical compositions can be administered orally, intranasally,  
5 parenterally or by inhalation therapy, and may take the form of tablets, lozenges, granules, capsules, pills, ampoules, suppositories or aerosol form. They may also take the form of suspensions, solutions and emulsions of the active ingredient in aqueous or non-aqueous diluents, syrups, granulates or powders. In addition to an agent of the present invention, the pharmaceutical compositions can also contain other pharmaceutically active compounds or a  
10 plurality of compounds of the invention.

[00211] More particularly, an agent of the present invention also referred to herein as the active ingredient, may be administered for therapy by any suitable route including, but not limited to, oral, rectal, nasal, topical (including, but not limited to, transdermal, aerosol, buccal and sublingual), vaginal, parental (including, but not limited to, subcutaneous, intramuscular,  
15 intravenous and intradermal) and pulmonary. It is also appreciated that the preferred route varies with the condition and age of the recipient, and the disease being treated.

[00212] Ideally, the agent should be administered to achieve peak concentrations of the active compound at sites of disease. This may be achieved, for example, by the intravenous injection of the agent, optionally in saline, or by oral administration, for example, as a tablet,  
20 capsule or syrup containing the active ingredient.

[00213] Desirable blood levels of the agent may be maintained by a continuous infusion to provide a therapeutic amount of the active ingredient within disease tissue. The use of operative combinations is contemplated to provide therapeutic combinations requiring a lower total dosage of each component than may be required when each individual therapeutic  
25 compound or drug is used alone, thereby reducing adverse effects.

#### **D. Exemplary Co-administration Routes and Dosing Considerations**

[00214] The invention also includes methods involving co-administration of the compounds described herein with one or more additional active agents. Indeed, it is a further aspect of this invention to provide methods for enhancing prior art therapies and/or pharmaceutical  
30 compositions by co-administering a compound of this invention. In co-administration

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procedures, the agents may be administered concurrently or sequentially. In one embodiment, the compounds described herein are administered prior to the other active agent(s). The pharmaceutical formulations and modes of administration may be any of those described above. In addition, the two or more co-administered chemical agents, biological agents or  
5 radiation may each be administered using different modes or different formulations.

[00215] The agent or agents to be co-administered depend on the type of condition being treated. For example, when the condition being treated is cancer, the additional agent can be a chemotherapeutic agent or radiation. When the condition being treated is an immune disorder, the additional agent can be an immunosuppressant or an anti-inflammatory agent. When the  
10 condition being treated is chronic inflammation, the additional agent can be an anti-inflammatory agent. The additional agents to be co-administered, such as anticancer, immunosuppressant, anti-inflammatory, can be any of the well-known agents in the art, including, but not limited to, those that are currently in clinical use. The determination of appropriate type and dosage of radiation treatment is also within the skill in the art or can be  
15 determined with relative ease.

[00216] Treatment of the various conditions associated with abnormal apoptosis is generally limited by the following two major factors: (1) the development of drug resistance and (2) the toxicity of known therapeutic agents. In certain cancers, for example, resistance to chemicals and radiation therapy has been shown to be associated with inhibition of apoptosis. Some  
20 therapeutic agents have deleterious side effects, including non-specific lymphotoxicity, renal and bone marrow toxicity.

[00217] The methods described herein address both these problems. Drug resistance, where increasing dosages are required to achieve therapeutic benefit, is overcome by co-administering the compounds described herein with the known agent.

### EXAMPLES

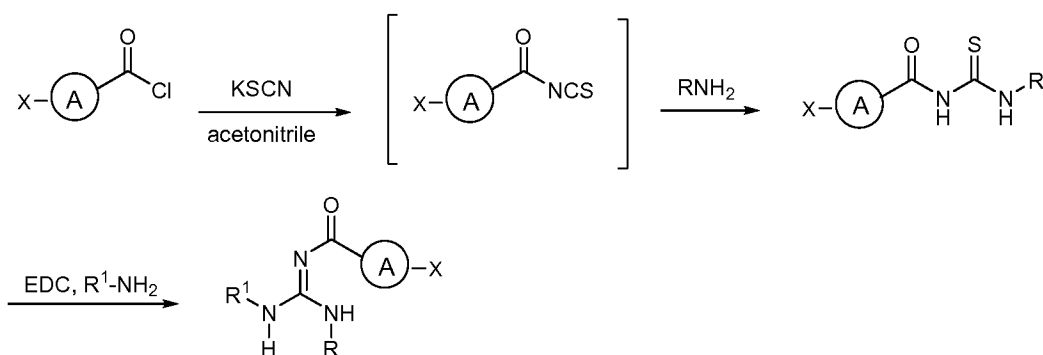
25 [00218] The invention now being generally described, will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

**EXAMPLE 1 – PREPARATION OF INDAZOLE GUANIDINE COMPOUNDS**

[00219] Described below is an exemplary general synthetic procedure for making acyl guanidine compounds having an indazole group, along with an exemplary synthetic procedure for making the specific indazole guanidine compound (*S*)-*N*-(((6-Chloro-1H-indazol-3-yl)amino)((1-methoxypropan-2-yl)amino)methylene)-3,4-difluorobenzamide.

**Part I: General Method for Making Acyl Guanidine Compounds**

**SCHEME 2**



[00220] Acyl guanidines having an indazole group can be prepared from an acid chloride, an amino-indazole, and a second amine using a three-step, 2-pot procedure. First, the requisite acid chloride is combined with a slight molar excess of potassium thiocyanate in a polar aprotic solvent (such as acetonitrile) at a temperature in the range of from about 0 °C to room temperature. The resulting mixture is stirred for a time period ranging from 15 minutes to 18 hours to provide a reaction mixture containing the acyl isothiocyanate synthetic intermediate compound. This reaction mixture may be used directly in the next reaction or filtered to remove the potassium chloride generated during this first step.

[00221] In a second step, the acyl isothiocyanate compound is combined with an amino-indazole (which may be dissolved in a solvent) to provide a reaction mixture that is stirred for a time period ranging from 15 minutes to 2 hours to produce an acyl thiourea product. The acyl thiourea product may precipitate from the reaction mixture and be collected by filtration. Water may be added to the reaction mixture (typically in amount equal to the volume of organic solvent) to facilitate collection of the acyl thiourea product. The acyl thiourea product is dried *in vacuo* at approximately 50 °C.

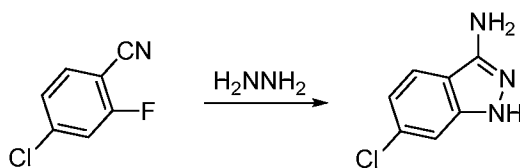
- 65 -

[00222] In a third step, the acyl thiourea product is combined with a coupling agent (such as *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide (EDC)) and a second amine to produce the acyl guanidine containing an indazole group. All starting materials for this reaction may be combined prior to heating the reaction mixture or the EDC may be added last, once the temperature of the reaction mixture has been raised. Alternatively, the second amine may be added last after combining the thiourea and the EDC. Once all the starting materials have been combined, the reaction mixture is generally stirred for a time period ranging from about 30 minutes to about 24 hours while the reaction mixture is heated to a temperature ranging from about 45 °C to about 70 °C.

10 **Part II: Exemplary Synthetic Procedure for Preparing (*S*)-*N*-((((6-Chloro-1H-indazol-3-yl)amino)((1-methoxypropan-2-yl)amino)methylene)-3,4-difluorobenzamide (1)**

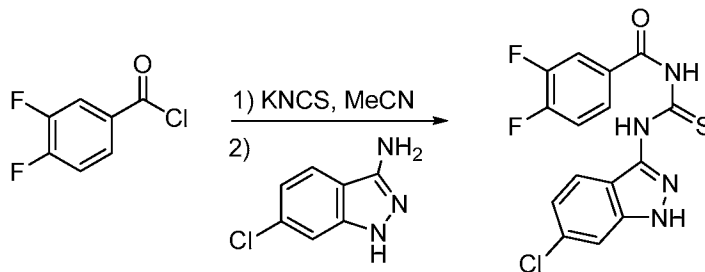
[00223] The title compound was prepared according to the procedures described below.

**Step A: Preparation of 6-Chloro-1H-indazol-3-amine**



15 [00224] Hydrazine (1.13 g, 35.3 mmol) was dissolved in isopropanol (80 mL) and treated with 4-chloro-2-fluorobenzonitrile (5 g, 32.1 mmol). The resulting solution was stirred at 80 °C for 1 day. Upon removal from heat, a white solid precipitated. This solid was collected by filtration and washed with isopropyl alcohol (IPA) then diethyl ether and dried *in vacuo* at 50 °C to give the title compound as a white solid (2.45 g).

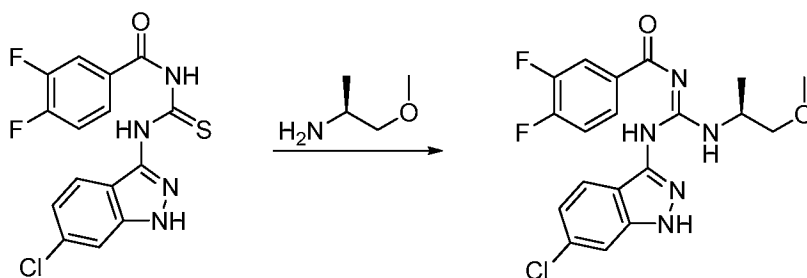
20 **Step B: Preparation of *N*-[(6-Chloro-1H-indazol-3-yl)carbamothioyl]-3,4-difluorobenzamide**



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[00225] 3,4-Difluorobenzoyl chloride (2581 mg, 14.618 mmol) was dissolved in acetonitrile (70 mL) and potassium thiocyanate (1563 mg, 16.08 mmol) was added. The resulting slurry was stirred at room temperature for approximately 30 minutes forming a pale yellow precipitate, then 6-chloro-2H-indazol-3-amine (2450 mg, 14.62 mmol) was added in one portion. The reaction mixture was stirred at room temperature for an additional 30 minutes, and then water (100 mL) was added. After stirring the resulting mixture for 30 minutes, the mixture was filtered then the pad was dried overnight at 50 °C *in vacuo* to provide the title compound as a yellow solid.

**Step C: Preparation of (S)-N-(((6-Chloro-1H-indazol-3-yl)amino)((1-methoxypropan-2-yl)amino)methylene)-3,4-difluorobenzamide (1)**



[00226] *N*-(((6-Chloro-1H-indazol-3-yl)carbamothioyl)-3,4-difluorobenzamide (5.36 g, 14.6 mmol) and *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide (EDC) (3.08 g, 16.1 mmol) were combined in tetrahydrofuran (THF) (120 mL), and (*S*)-2-methoxyisopropylamine (1.95 g, 21.9 mmol) was added. The resulting reaction mixture then was heated to 60 °C for 1 hr. HPLC indicated no starting material remaining. Next, the reaction mixture was allowed to cool, concentrated to ~40 mL, and diluted with ethyl acetate. The diluted mixture was washed with dilute aqueous NH<sub>4</sub>Cl twice, then with water, and then with brine. After the second wash, a solid formed in the organic layer. After the brine wash, the organic layer was filtered through a coarse filter, removing a small amount of white solid. The filtrate was dried over anhydrous sodium sulfate, and removal of the drying agent by filtration gave a clear filtrate, which was concentrated to dryness giving a yellow solid. The yellow solid was combined with acetonitrile (300 mL) and the resulting mixture was heated to reflux. The hot solution was filtered to collect a very small amount of white solid, then the filtrate was allowed to cool. Crystals started to form. Next, the mixture was concentrated slightly on a rotary evaporator, then filtered to give a thin pad of white needles. The filtrate was further concentrated, cooled to 0 °C, and more solid was collected by another filtration. The solids from the crystallization were

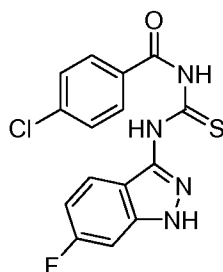
- 67 -

combined to give the title compound (5.25 g, 89% yield).  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  13.4 (s, 1H), 13.0 (s, 1H), 8.82 (m, 1H), 8.0 (m, 2H), 7.85 (d, 1H), 7.6 (s, 1H), 7.5 (m, 1H), 7.2 (m, 1H), 4.6 (m, 1H), 3.5 (s, 2H), 3.3 (s, 3H), 1.3 (d, 3H). MS: calc. = 421.83; obs. = 420, 422. HPLC (Method E): retention time was 6.94 minutes.

5 **EXAMPLE 2 – PREPARATION OF 4-CHLORO-*N*-(((6-FLUORO-1H-INDAZOL-3-YL)AMINO)((2-HYDROXY-2-METHYLPROPYL)AMINO)METHYLENE)BENZAMIDE (2)**

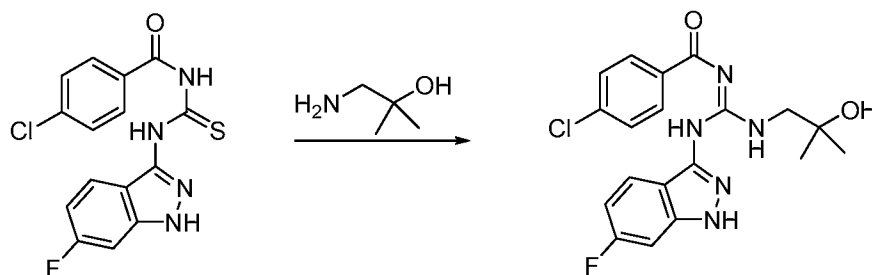
[00227] The title compound was prepared according to the procedures described below.

**Part I: Preparation of 4-Chloro-*N*-((6-fluoro-1H-indazol-3-yl)carbamothioyl)benzamide**



10 [00228] The title compound was prepared based on the procedures described in Example 1.

**Part II: Preparation of 4-Chloro-*N*-((6-fluoro-1H-indazol-3-ylamino)((2-hydroxy-2-methylpropyl)amino)methylene)benzamide (2)**



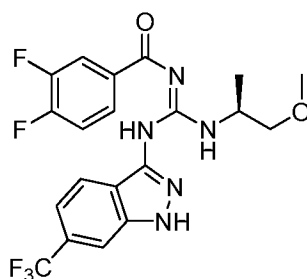
15 [00229] 4-Chloro-*N*-((6-fluoro-1H-indazol-3-yl)carbamothioyl)benzamide (0.2 g, 0.57 mmol) and EDC (0.12 g, 0.63 mmol) were combined in dry THF (5 mL) and treated with 1-amino-2-methyl-propan-2-ol (77 mg, 0.86 mmol) then heated to 60 °C for 4 hours. Next, the reaction mixture was allowed to cool, concentrated onto silica gel, and chromatographed eluting with 20-70% ethyl acetate in hexanes to provide the title compound as a brown solid (63 mg, 27%). MS: calc. = 403.84; obs. = 402 (in negative ion mode). HPLC (Method E):  
20 retention time was 4.3 minutes.

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**EXAMPLE 3 – PREPARATION OF (*S*)-3,4-DIFLUORO-*N*-(((1-METHOXYPROPAN-2-  
YL)AMINO))((6-(TRIFLUOROMETHYL)-1H-INDAZOL-3-YL)AMINO)METHYLENE)BENZAMIDE (3)  
AND (*S*)-3,4-DIFLUORO-*N*-(((1-METHOXYPROPAN-2-YL)AMINO))((6-(TRIFLUOROMETHYL)-1H-  
INDAZOL-3-YL)AMINO)METHYLENE)BENZAMIDE SULFURIC ACID SALT (4)**

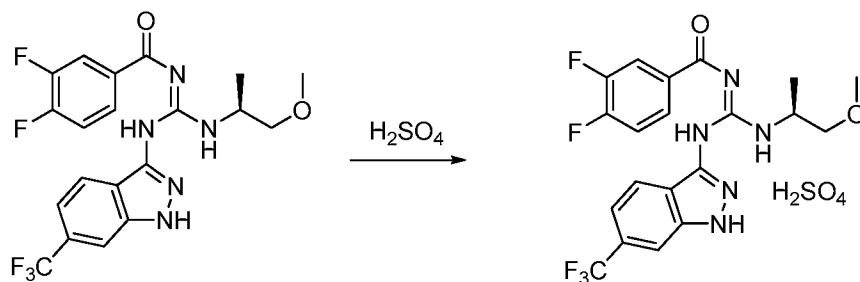
5 [00230] The title compound was prepared according to the procedures described below.

**Part I: Preparation of (*S*)-3,4-Difluoro-*N*-(((1-methoxypropan-2-yl)amino))((6-(trifluoromethyl)-1H-indazol-3-yl)amino)methylene)benzamide (3)**



10 [00231] The title compound was prepared based on the procedures described in Example 1.  
<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 13.50 (s, 1H), 13.33 (s, 1H), 8.82 (d, 1H), 8.03 (m, 2H), 7.90 (m, 2H), 7.48 (m, 2H), 4.60 (m, 1H), 3.51 (d, 2H), 3.30 (s, 3H), 1.26 (d, 3H). MS: calc. = 455.38; obs. = 456.08. HPLC (Method B): retention time was 6.54 minutes.

**Part II: Preparation of (*S*)-3,4-Difluoro-*N*-(((1-methoxypropan-2-yl)amino))((6-(trifluoromethyl)-1H-indazol-3-yl)amino)methylene)benzamide Sulfuric Acid Salt (4)**



15 [00232] (*S*)-3,4-Difluoro-*N*-(((1-methoxypropan-2-yl)amino))((6-(trifluoromethyl)-1H-indazol-3-yl)amino)methylene)benzamide (105 mg) was dissolved in ethyl acetate (0.5 mL) to give a yellow solution, then treated dropwise with 100 μL of a solution of sulfuric acid (112 mg) in ethyl acetate (300 μL). The solution turned colorless, then slightly cloudy. It was  
20 allowed to stand at room temperature in a glass vial with a loose cap overnight. A precipitate

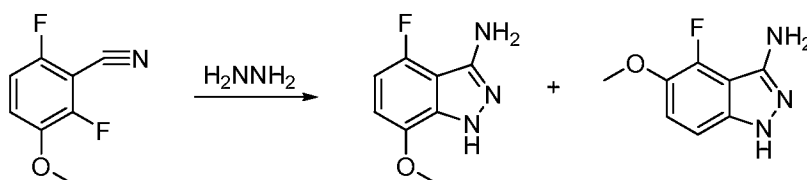
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formed and was collected by filtration, then rinsed with diethyl ether and dried *in vacuo* to give the title compound as a white solid, m.p. = 183-186 °C.

**EXAMPLE 4 – PREPARATION OF *N*-((TERT-BUTYLAMINO)((4-FLUORO-7-METHOXY-1H-INDAZOL-3-YL)AMINO)METHYLENE)-3,4-DIFLUOROBENZAMIDE**

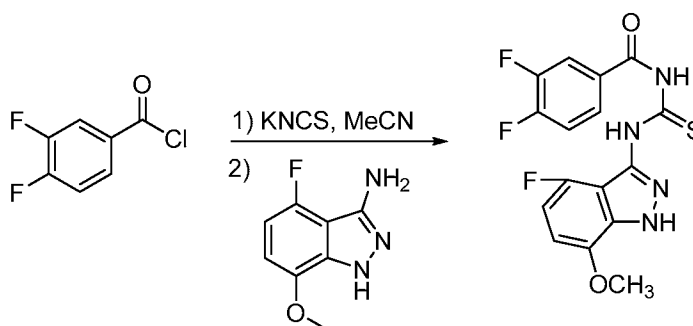
5 [00233] The title compound was prepared according to the procedures described below.

**Part I: Preparation of 4-Fluoro-7-methoxy-1H-indazol-3-amine**



[00234] 2,6-Difluoro-3-methoxy-benzonitrile (1 g, 5.9 mmol) was dissolved in ethanol (20 mL) and treated with hydrazine (0.21 g, 6.5 mmol) in a glass vial. The vial was capped and placed on a shaker then heated to 75 °C overnight. Then, the mixture was evaporated to dryness and the product was obtained as a 1:1 mixture of isomers.

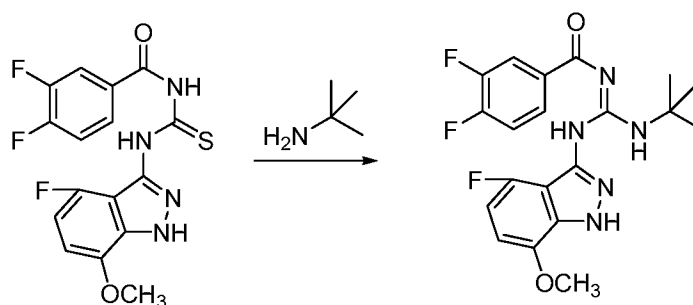
**Part II: Preparation of 3,4-Difluoro-*N*-((4-fluoro-7-methoxy-1H-indazol-3-yl)carbamothioyl)benzamide**



15 [00235] 3,4-Difluorobenzoyl chloride (487 mg, 2.76 mmol) was dissolved in acetonitrile (30 mL) and potassium thiocyanate (295 mg, 3.04 mmol) was added. This mixture was stirred at room temperature for approximately 90 minutes then the indazole (from Part I above) was added as a mixture of isomers (500 mg, 2.76 mmol). After stirring for an additional 30 minutes at room temperature, water (30 mL) was added and the mixture was filtered. The resulting solid was dried at 50 °C *in vacuo* to give the title compound (1.46 g).

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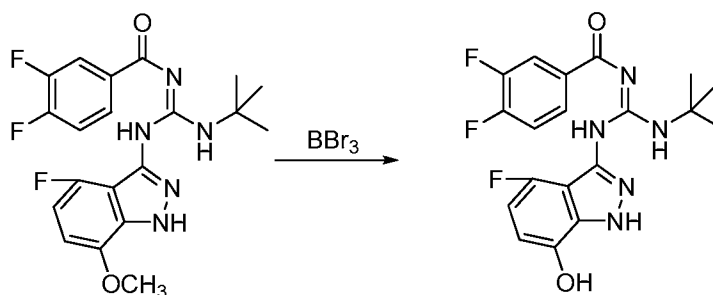
**Part III: Preparation of *N*-((tert-Butylamino)((4-fluoro-7-methoxy-1H-indazol-3-yl)amino)methylene)-3,4-difluorobenzamide**



**[00236]** 3,4-Difluoro-*N*-((4-fluoro-7-methoxy-1H-indazol-3-yl)carbamothioyl)benzamide

(200 mg, 0.53 mmol) and EDC (111 mg, 0.58 mmol) were combined in dry THF (5 mL), and then tert-butylamine (38 mg, 0.53 mmol) was added. The resulting mixture was heated to 55 °C for approximately 30 minutes, and then concentrated onto silica gel. Chromatography eluting with 10-30% ethyl acetate in hexanes provided the title compound as a white solid (90 mg, 41%). MS: calc. = 419.4; obs. = 420.1. HPLC (Method D): retention time was 2.98 minutes.

**EXAMPLE 5 – PREPARATION OF *N*-((TERT-BUTYLAMINO)((4-FLUORO-7-HYDROXY-1H-INDAZOL-3-YL)AMINO)METHYLENE)-3,4-DIFLUOROBENZAMIDE**



**[00237]** *N*-((tert-Butylamino)((4-fluoro-7-methoxy-1H-indazol-3-yl)amino)methylene)-3,4-

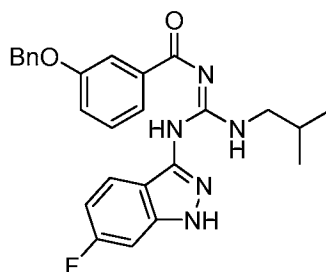
difluorobenzamide (115 mg, 0.27 mmol) was dissolved in dichloromethane (DCM) (0.2 mL) under nitrogen and BBr<sub>3</sub> in DCM (1M, 2.7 mL) was added. The resulting mixture was stirred at room temperature overnight then cooled in an ice-bath and quenched with methanol. The resulting mixture was diluted with ethyl acetate, washed with water, washed with brine, and then dried (MgSO<sub>4</sub>). Chromatography on silica gel eluting with 50-90% ethyl acetate in hexanes provide the title compound (50 mg, 45%).

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**EXAMPLE 6 – PREPARATION OF *N*-(((6-FLUORO-1H-INDAZOL-3-YL)AMINO)(ISOBUTYLAMINO)METHYLENE)-3-HYDROXYBENZAMIDE**

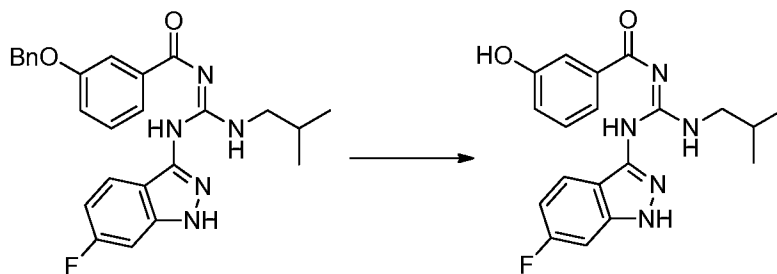
[00238] The title compound was prepared according to the procedures described below.

**Part I: Preparation of (*Z*)-3-(Benzyloxy)-*N*-(((6-fluoro-1H-indazol-3-yl)amino)(isobutylamino)methylene)benzamide**



[00239] The title compound was prepared based on the procedures described in Example 1.

**Part II: Preparation of *N*-(((6-Fluoro-1H-indazol-3-yl)amino)(isobutylamino)methylene)-3-hydroxybenzamide**



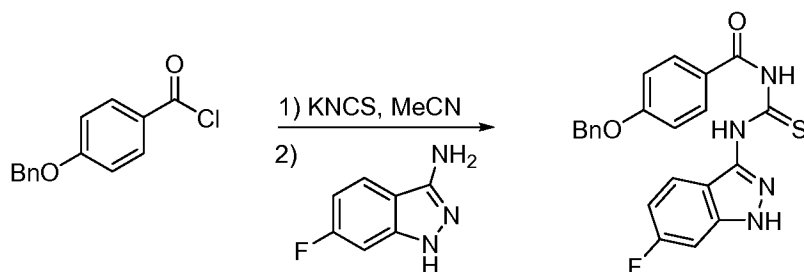
[00240] (*Z*)-3-(Benzyloxy)-*N*-(((6-fluoro-1H-indazol-3-yl)amino)(isobutylamino)methylene) benzamide (160 mg, 0.35 mmol) was dissolved in methanol (8 mL), and ammonium formate (219 mg, 3.5 mmol) was added. A slow stream of nitrogen gas was then bubbled through the reaction mixture for about 30 seconds, and then a small spatula-full of 10% palladium on carbon was added to the reaction mixture. The resulting mixture was shaken at 50 °C for 1 h, and then cooled back to room temperature. Any pressure buildup in the vial was released by piercing the septum with a needle. The mixture was filtered through a pad of celite, chasing with a copious amount of methanol. The filtrate was concentrated onto silica gel, and purified by chromatography to give the title compound (56 mg, 44%).

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**EXAMPLE 7 – PREPARATION OF (S)-N-(((6-FLUORO-1H-INDAZOL-3-YL)AMINO)((1-METHOXYPROPAN-2-YL)AMINO)METHYLENE)-4-HYDROXYBENZAMIDE**

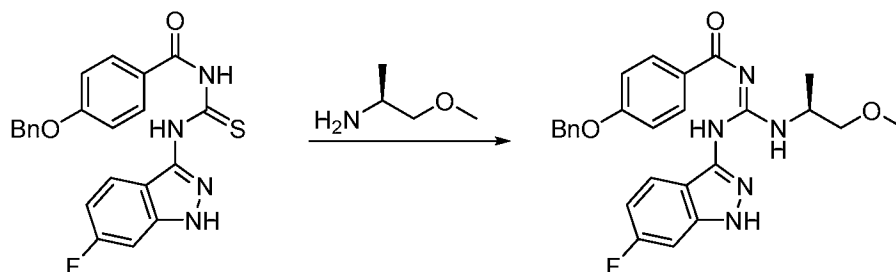
[00241] The title compound was prepared according to the procedures described below.

**Part I: Preparation of 4-(Benzyloxy)-N-((6-fluoro-1H-indazol-3-yl)carbamothioyl)benzamide**



[00242] The title compound was prepared based on the procedures described in Example 1, Step B.

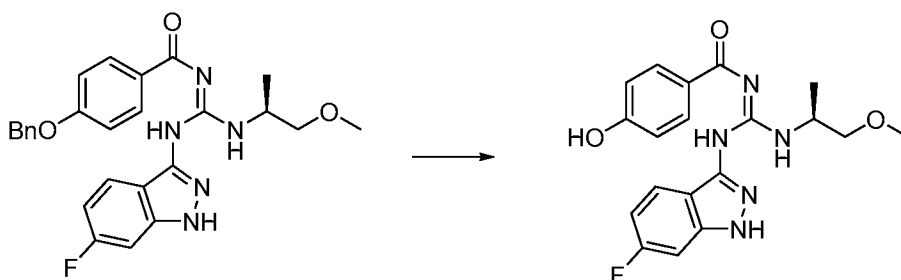
**Part II: Preparation of (S)-4-(Benzyloxy)-N-(((6-fluoro-1H-indazol-3-yl)amino)((1-methoxypropan-2-yl)amino)methylene)benzamide**



[00243] 4-(Benzyloxy)-N-((6-fluoro-1H-indazol-3-yl)carbamothioyl)benzamide (220 mg, 0.523 mmol) and EDC (110 mg, 0.576 mmol) were added to a vial, followed by THF (6 mL) and 3-methoxypropyl-2-amine (70 mg, 0.78 mmol). The reaction mixture was shaken at 50 °C for 30 minutes. Silica gel was added to the crude mixture, and the solvent was removed under vacuum. The crude material was purified by chromatography to give the title compound (150 mg, 0.315 mmol).

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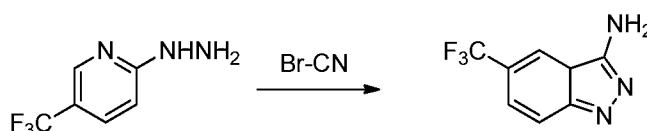
**Part III: Preparation of (S)-N-(((6-Fluoro-1H-indazol-3-yl)amino)((1-methoxypropan-2-yl)amino)methylene)-4-hydroxybenzamide**



**[00244]** (S)-4-(Benzyloxy)-N-(((6-fluoro-1H-indazol-3-yl)amino)((1-methoxypropan-2-

5 yl)amino)methylene)benzamide (150 mg, 0.315 mmol) was dissolved in methanol (8 mL), and ammonium formate (199 mg, 3.15 mmol) was added. A slow stream of nitrogen gas was then bubbled through the reaction mixture for about 30 seconds, and a catalytic amount of 10% palladium on carbon was added. The resulting mixture was shaken at 50 °C for 1 h, and then cooled back to room temperature. Any pressure buildup in the vial was released by piercing  
10 the septum with a needle. Next, the mixture was filtered through a pad of celite, and the pad was rinsed with a copious amount of methanol. The filtrate was concentrated onto silica gel, and the product purified by chromatography to give the title compound (36 mg, 30%).

**EXAMPLE 8 – PREPARATION OF 6-(TRIFLUOROMETHYL)-[1,2,4]TRIAZOLO[4,3-A]PYRIDIN-3-AMINE**



**[00245]** To a solution of [5-(trifluoromethyl)-2-pyridyl]hydrazine (3.895 g, 21.99 mmol) in methanol (100 mL) was added cyanogen bromide solid (5.82 g, 54.9 mmol) all at once. The reaction mixture was stirred at room temperature overnight. Then, the resulting solid was filtered off and rinsed with a small amount of 1:1 EtOAc : MeOH, giving the indazole as the  
20 hydrobromide salt. The resulting solid salt (5.07 g) was dissolved in 250 mL of MeOH and treated with MP-carbonate resin (17.49 g; Aldrich catalog number 540293, 2.5-3.5 mmol/g). This mixture was stirred overnight and then the resin was filtered off, rinsing with alternating methanol and methylene chloride. The solvents were removed under vacuum to give the title

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compound (3.71 g, 83.4% yield) as a yellow/brown solid.  $^1\text{H}$  NMR (400MHz, DMSO- $d_6$ )  $\delta$  8.77 (m, 1H), 7.62 (m, 1H), 7.24 (m, 1H), 6.74 (br s, 2H).

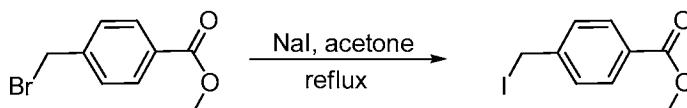
**EXAMPLE 9 – PREPARATION OF (S)-((4-**

**((PHOSPHONOOXY)METHYL)BENZOYL)OXY)METHYL 3-(2-(3,4-DIFLUOROBENZOYL)-3-(1-**

5 **METHOXYPROPAN-2-YL)GUANIDINO)-6-(TRIFLUOROMETHYL)-1H-INDAZOLE-1-CARBOXYLATE (5)**

[00246] The title compound was prepared according to the procedures described below.

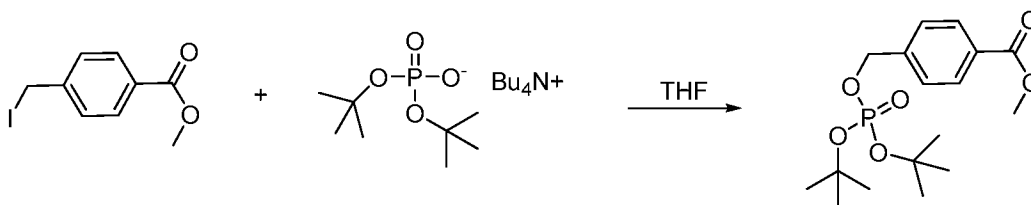
**Part I: Preparation of Methyl 4-(iodomethyl)benzoate**



10 [00247] Methyl 4-bromomethylbenzoate (5 g, 21.8 mmol) was dissolved in acetone (110 mL) and sodium iodide (6.54 g, 43.6 mmol) was added. The reaction mixture was heated to reflux for 3 hours, then concentrated *in vacuo*. The resulting residue was dissolved in EtOAc, and the solution was washed with a sodium thiosulfate solution (1% aqueous solution) then brine, then it was dried over sodium sulfate, and concentrated *in vacuo* to provide a crude

15 product that was purified by chromatography (gradient; 9:1 hexanes:EtOAc to 8:2 hexanes:EtOAc) to give the title compound (5.05 g, 84% yield).  $^1\text{H}$  NMR (DMSO- $D_6$ )  $\delta$  7.84 (d, 2H), 7.53 (d, 2H), 4.63 (s, 2H), 3.80 (s, 3H).

**Part II: Preparation of Methyl 4-(((di-tert-butoxyphosphoryl)oxy)methyl)benzoate**



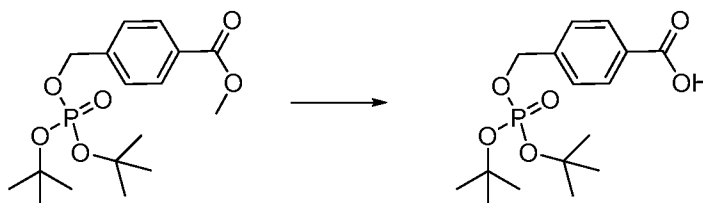
20 [00248] Methyl 4-(iodomethyl)benzoate (5.05 g, 18.29 mmol) and tetrabutylammonium di-tert-butyl phosphate (8.26 g, 18.29 mmol) were dissolved in THF (183 mL) and the reaction mixture was stirred at room temperature for 18 h. Then, the crude product was partitioned between water and EtOAc. The organic phase was then washed with brine, dried over sodium sulfate, and then concentrated onto silica gel and purified by chromatography (gradient: 85:15

25 hexanes:EtOAc to 4:6 hexanes:EtOAc) to give the title compound as a white solid (4.30 g, 66%

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yield).  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  7.95 (d, 2H), 7.48 (d, 2H), 4.98 (d, 2H), 3.83 (s, 3H), 1.37 (s, 18 H).

### Part III: Preparation of 4-(((di-tert-Butoxyphosphoryl)oxy)methyl)benzoic acid



- 5 [00249] Methyl 4-(((di-tert-butoxyphosphoryl)oxy)methyl)benzoate (4.3 g, 12.0 mmol) was dissolved in methanol (120 mL) and lithium hydroxide (474 mg, 19.80 mmol) dissolved in 10 mL water was added. The reaction mixture was stirred for 4 h at 50° C. Then, the solvent was removed *in vacuo*, and the crude product was used in the next reaction without purification.

### Part IV: Preparation of 4-(((di-tert-Butoxyphosphoryl)oxy)methyl)benzoic acid silver salt



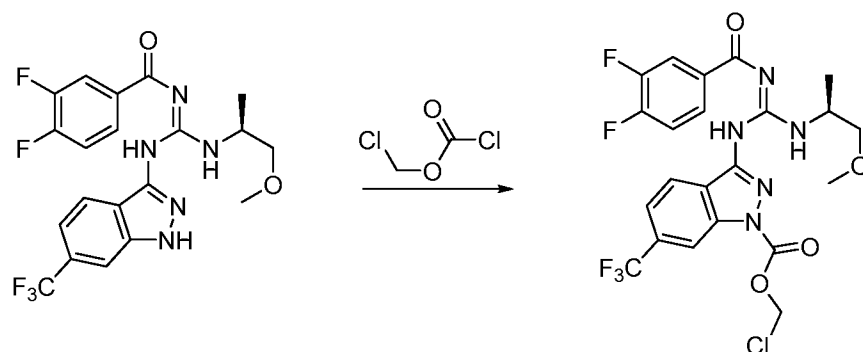
10

- [00250] Lithium 4-(((di-tert-butoxyphosphoryl)oxy)methyl)benzoate (4.13 g, 11.79 mmol) was suspended in water (118 mL). Silver nitrate (2 g, 11.79 mmol) was added, and the reaction mixture was stirred for 2 h. The white precipitate was then collected by filtration and held under heated vacuum overnight delivering a product which had changed to a black solid (2.43 g, 46% yield).

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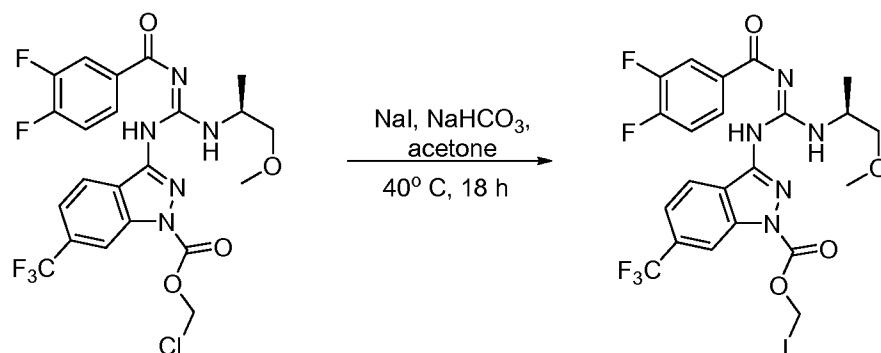
**Part V: Preparation of (S)-Chloromethyl 3-(2-(3,4-difluorobenzoyl)-3-(1-methoxypropan-2-yl)guanidino)-6-(trifluoromethyl)-1H-indazole-1-carboxylate**



**[00251]** (S)-3,4-Difluoro-N-(((1-methoxypropan-2-yl)amino)((6-(trifluoromethyl)-1H-

indazol-3-yl)amino)methylene)benzamide (4 g, 8.78 mmol) was dissolved in THF (30 mL) and the solution was cooled to -40°C. Next, the solution was treated with Hunig's base (3.06 mL, 17.57 mmol) followed by chloromethylchloroformate (1.87 mL, 21.08 mmol). The resulting mixture was stirred at -40 °C for 20 minutes, then the bath was taken away and as soon as the reaction was at room temperature the crude mixture was concentrated onto silica gel and purified by chromatography eluting with dichloromethane to give the title compound (4.70 g, 98% yield). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 12.22 (bs, 1H), 8.92 (d, 1H), 8.35 (s, 1H), 8.02 (m, 3H), 7.72 (m, 2H), 6.25 (s, 2H), 4.53 (m, 1H), 3.52 (d, 2H), 3.32 (s, 3H), 1.30 (d, 3H).

**Part VI: Preparation of (S)-Iodomethyl 3-(2-(3,4-difluorobenzoyl)-3-(1-methoxypropan-2-yl)guanidino)-6-(trifluoromethyl)-1H-indazole-1-carboxylate**

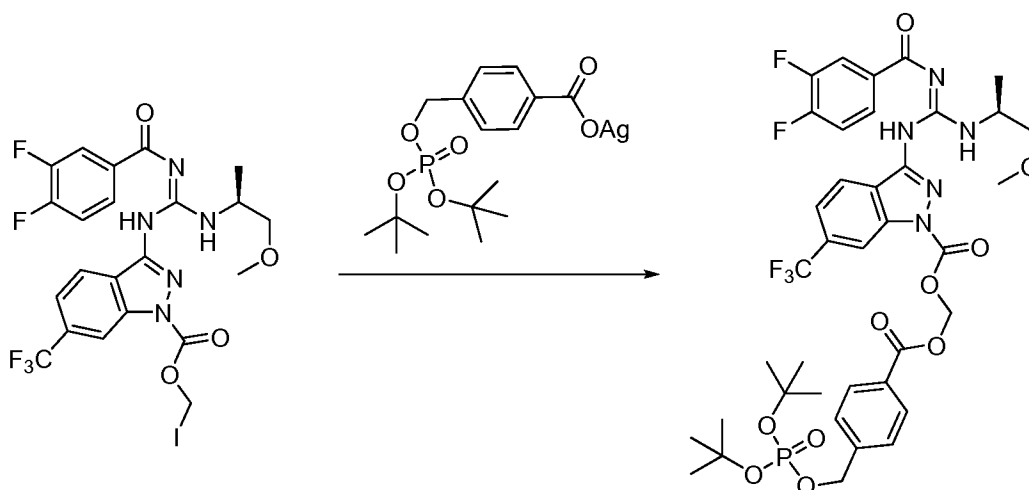


**[00252]** (S)-Chloromethyl 3-(2-(3,4-difluorobenzoyl)-3-(1-methoxypropan-2-yl)guanidino)-6-(trifluoromethyl)-1H-indazole-1-carboxylate (4.7 g, 8.58 mmol) was suspended in acetone (120 mL), and sodium iodide (2.57 g, 17.16 mmol) was added followed by sodium bicarbonate

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(72 mg, 0.86 mmol). The reaction mixture was heated to 40 °C for 18 h. Next, EtOAc(700 mL) was added to the reaction mixture, and the mixture was washed with sodium bicarbonate solution, then with 1% sodium thiosulfate solution until the organic phase was clear. The organic phase was dried over sodium sulfate, then concentrated *in vacuo* to provide the crude product, which was used in the next step without further purification.

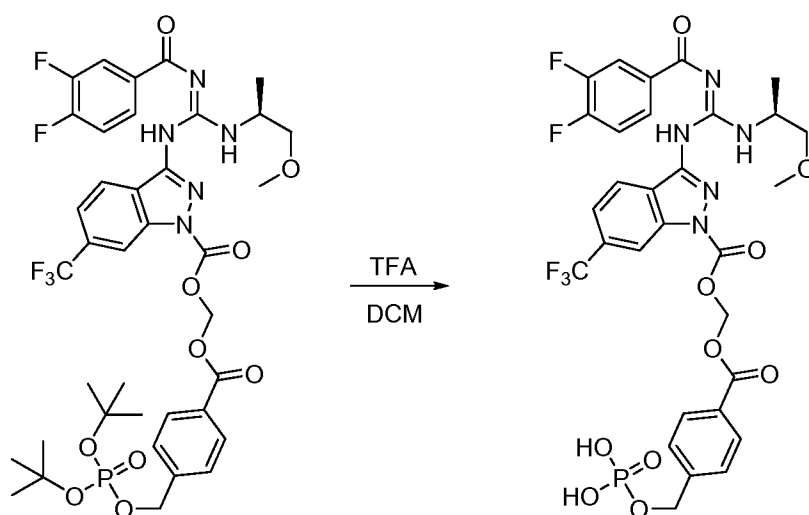
**Part VII: Preparation of (S)-((4-(((di-tert-Butoxyphosphoryl)oxy)methyl)benzoyl)oxy)methyl 3-(2-(3,4-difluorobenzoyl)-3-(1-methoxypropan-2-yl)guanidino)-6-(trifluoromethyl)-1H-indazole-1-carboxylate**



- 10 **[00253]** ((4-(((di-tert-Butoxyphosphoryl)oxy)methyl)benzoyl)oxy)silver (2.0 g, 4.42 mmol), and (S)-iodomethyl 3-(2-(3,4-difluorobenzoyl)-3-(1-methoxypropan-2-yl)guanidino)-6-(trifluoromethyl)-1H-indazole-1-carboxylate (2.02 g, 3.16 mmol) were suspended in THF (33 mL) and the reaction mixture was stirred at room temperature for two hours. The crude material was then concentrated onto silica gel and purified by chromatography to give the title
- 15 compound as a yellow solid (600 mg, 22% yield). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 8.89 (bs, 1H), 8.33 (m, 1H), 8.00 (m, 5H), 7.72 (d, 1H), 7.51 (d, 2H), 6.35 (m, 2H), 4.97 (m, 2H), 4.50 (m, 1H), 3.48 (m, 2H), 3.32 (s, 3H), 1.35 (s, 18H), 1.27 (d, 3H). MS, 878.21 (parent + Na<sup>+</sup>); HPLC (method B), retention time = 8.60 min.

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**Part VIII: Preparation of (S)-((4-((Phosphonooxy)methyl)benzoyl)oxy)methyl 3-(2-(3,4-difluorobenzoyl)-3-(1-methoxypropan-2-yl)guanidino)-6-(trifluoromethyl)-1H-indazole-1-carboxylate (5)**



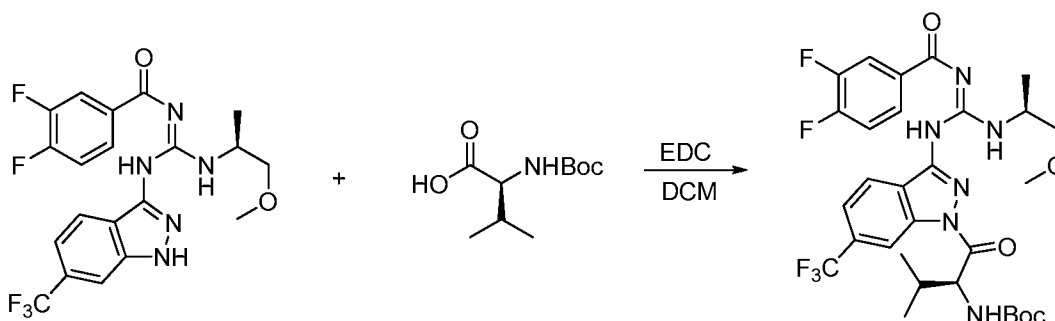
- 5 **[00254]** (S)-((4-(((di-tert-Butoxyphosphoryl)oxy)methyl)benzoyl)oxy)methyl 3-(2-(3,4-difluorobenzoyl)-3-(1-methoxypropan-2-yl)guanidino)-6-(trifluoromethyl)-1H-indazole-1-carboxylate (570 mg, 0.67 mmol) was dissolved in DCM (20 mL), and trifluoroacetic acid (TFA) (6 mL, 120 eqvt) was added. The reaction was run for 4 h at room temperature, then the reaction mixture was concentrated *in vacuo*, and re-concentrated from methanol twice to
- 10 eliminate the TFA. The resulting yellow solid was slurried in 1:1 EtOAc:hexanes for 1 hour, then the slurry was filtered through a sintered glass funnel to give the title compound (400 mg, 90% pure by HPLC method B: retention time = 6.202 minutes). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 12.38 (bs, 1H), 8.87 (d, 1H), 8.30 (bs, 1H), 8.00 (m, 5H), 7.70 (d, 1H), 7.50 (m, 2H), 6.33 (m, 2H), 4.93 (m, 2H), 4.48 (m, 1H), 3.46 (m, 2H), 3.32 (s, 3H), 1.26 (d, 3H). MS: m/z = 742.32
- 15 (negative mode).

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**EXAMPLE 10** – PREPARATION OF *N*-(((1-((*S*)-2-AMINO-3-METHYLBUTANOYL)-6-(TRIFLUOROMETHYL)-1H-INDAZOL-3-YL)AMINO)(((*S*)-1-METHOXYPROPAN-2-YL)AMINO)METHYLENE)-3,4-DIFLUOROBENZAMIDE HYDROCHLORIDE SALT (6)

[00255] The title compound was prepared according to the procedures described below.

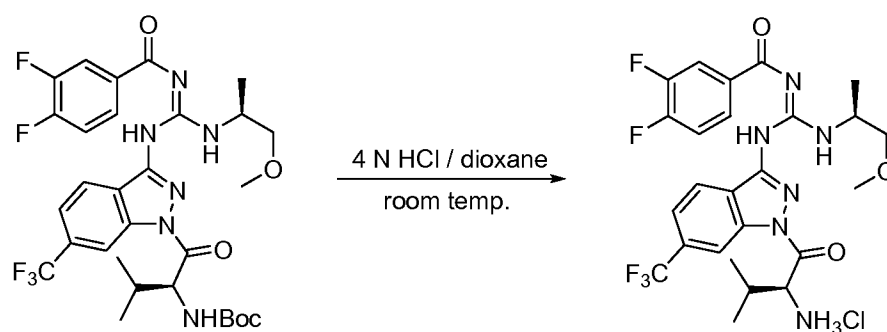
5 **Part I: Preparation of tert-Butyl ((*S*)-1-(3-(2-(3,4-difluorobenzoyl)-3-((*S*)-1-methoxypropan-2-yl)guanidino)-6-(trifluoromethyl)-1H-indazol-1-yl)-3-methyl-1-oxobutan-2-yl)carbamate**



[00256] EDC (1.768 g, 9.22 mmol), DCM (44 mL), and N-Boc-Valine (1.908 g, 8.78 mmol) were combined in a flask, and the mixture was stirred at room temperature for 10 minutes. To the flask was then added (*S*)-3,4-difluoro-*N*-(((1-methoxypropan-2-yl)amino)((6-(trifluoromethyl)-1H-indazol-3-yl)amino)methylene)benzamide (2.00g, 4.39 mmol) dissolved in the minimum amount of DCM, and the reaction mixture was stirred at room temperature overnight. An additional two equivalents of EDC and Boc-Val were then added, and the reaction mixture was stirred for an additional 5 h. The crude material was concentrated onto silica gel and purified by chromatography delivering the title compound as a light yellow solid (2.28 g, 79% yield). HPLC (method B) retention time = 8.45 min.

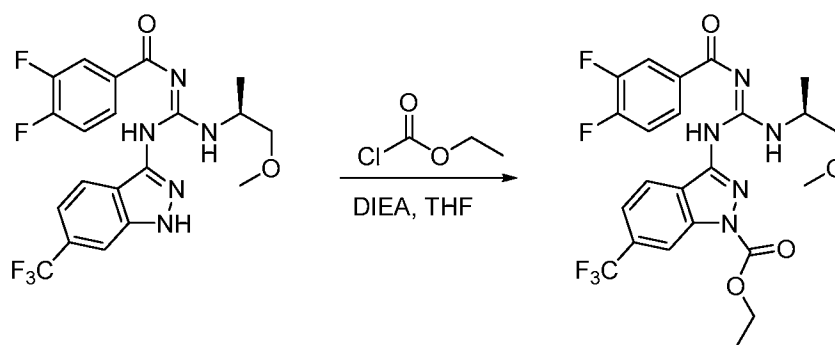
- 80 -

**Part II: Preparation of *N*-(((1-((*S*)-2-Amino-3-methylbutanoyl)-6-(trifluoromethyl)-1H-indazol-3-yl)amino)(((*S*)-1-methoxypropan-2-yl)amino)methylene)-3,4-difluorobenzamide Hydrochloride Salt (6)**



- 5 **[00257]** tert-Butyl ((*S*)-1-(3-(2-(3,4-difluorobenzoyl)-3-((*S*)-1-methoxypropan-2-yl)guanidino)-6-(trifluoromethyl)-1H-indazol-1-yl)-3-methyl-1-oxobutan-2-yl)carbamate (500 mg, 0.764 mmol) was dissolved in 4 N HCl in dioxane and the reaction was stirred at room temperature overnight. The solution was then concentrated *in vacuo* to provide the title compound as a yellow solid (369 mg, 72% yield). HPLC (method B) retention time = 5.5 min.
- 10 MS:  $m/z$  555.20 ( $M + 1$ ).

**EXAMPLE 11 – PREPARATION OF (*S*)-ETHYL 3-(2-(3,4-DIFLUOROBENZOYL)-3-(1-METHOXYPROPAN-2-YL)GUANIDINO)-6-(TRIFLUOROMETHYL)-1H-INDAZOLE-1-CARBOXYLATE (7)**



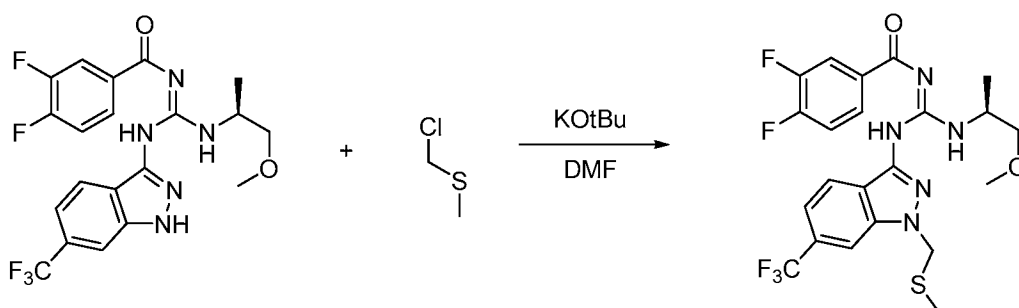
- 15 **[00258]** (*S*)-3,4-Difluoro-*N*-(((1-methoxypropan-2-yl)amino)((6-(trifluoromethyl)-1H-indazol-3-yl)amino)methylene)benzamide (500 mg, 1.10 mmol) was dissolved in THF (3 mL) and cooled to -40 °C. The solution was treated with Hunig's base (383  $\mu$ L, 2.20 mmol) followed by ethyl chloroformate (252  $\mu$ L, 2.64 mmol). The mixture was stirred at -40 °C for 20 minutes, then the bath was taken away and as soon as the reaction was at room temperature

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the crude mixture was concentrated, then suspended in EtOAc (400 mL) and washed once with citric acid solution, and twice with 1 M HCl, and then with brine. The solution was then dried over sodium sulfate, and concentrated onto silica gel and purified by chromatography (gradient: DCM to 9:1 DCM:MeOH) to provide the title compound (380 mg, 66% yield). MS: m/z

5 528.07 (M + 1). HPLC (method E) retention time = 10.3 min.

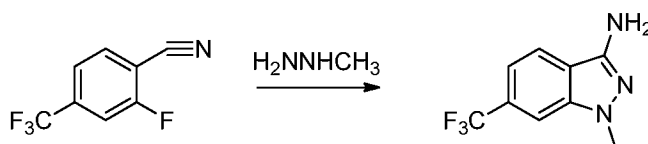
**EXAMPLE 12 – PREPARATION OF (S)-3,4-DIFLUORO-N-(((1-METHOXYPROPAN-2-YL)AMINO)((1-((METHYLTHIO)METHYL)-6-(TRIFLUOROMETHYL)-1H-INDAZOL-3-YL)AMINO)METHYLENE)BENZAMIDE (8)**



10 **[00259]** To solution of (S)-3,4-difluoro-N-(((1-methoxypropan-2-yl)amino)((6-(trifluoromethyl)-1H-indazol-3-yl)amino)methylene)benzamide (3.086 g, 6.77 mmol) in DMF (22 mL) at 0°C was added potassium tert-butoxide (10 mL of 1M solution in THF, 10.0 mmol). This mixture was stirred for 15 minutes then chloromethyl methyl sulfide (800 µL, 9.55 mmol) was added neat via syringe. The reaction mixture was allowed to warm to room temperature

15 while stirring overnight. The solution was then poured into 350 mL of ice water. After the ice melted, the resulting solid was collected by filtration and purified by chromatography (gradient, 0% EtOAc/DCM to 30% EtOAc/DCM) to provide the title compound as a white solid (3.88 g, 3.88 mmol, 85% yield). MS: m/z = 516 (M+H). HPLC (method E) retention time = 8.99 min.

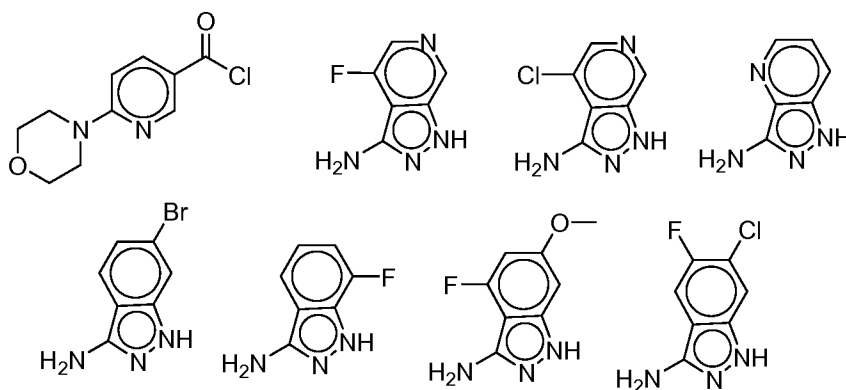
**EXAMPLE 13 – PREPARATION OF 1-METHYL-6-(TRIFLUOROMETHYL)-1H-INDAZOL-3-AMINE**



[00260] 2-Fluoro-4-(trifluoromethyl)benzonitrile (1 g, 5.29 mmol) was dissolved in isopropanol (20 mL) and treated with methylhydrazine (317 mg, 6.9 mmol). The resulting solution was stirred at 80 °C for 1 day and the reaction was followed by HPLC. Upon removal from heat, a white solid precipitated. This solid was collected by filtration and washed with isopropyl alcohol then dried *in vacuo* at 50 °C to give the product as a solid.

**EXAMPLE 14– ADDITIONAL INDAZOLE GUANIDINE COMPOUNDS & CHARACTERIZATION DATA**

[00261] Compounds in Table 2 below were prepared based on the procedures described in Examples 1-13 and procedures described in the detailed description. Starting materials can be obtained from commercial sources or readily prepared from commercially available materials. For example, the acid chloride compounds 4-chlorobenzoyl chloride, 3-chlorobenzoyl chloride, and 4-fluorobenzoyl chloride are commercially available, as well as the following acid chloride and amino-indazoles:



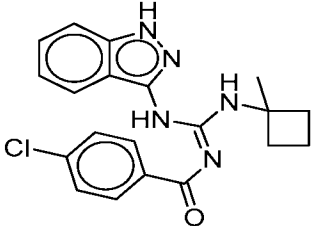
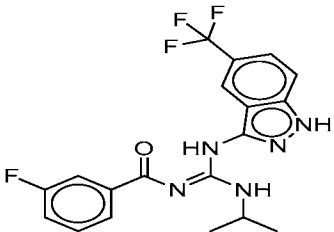
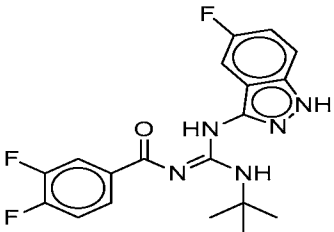
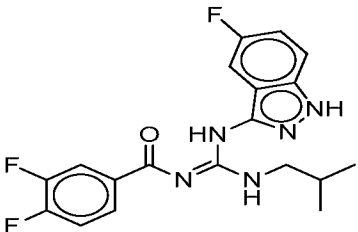
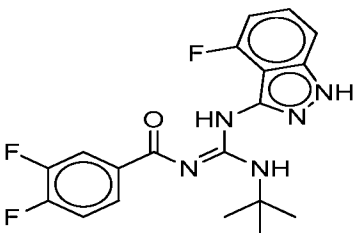
[00262] Furthermore, exemplary compounds were characterized by high performance liquid chromatography (HPLC), mass spectrometry (MS) and/or <sup>1</sup>H nuclear magnetic resonance spectroscopy. Unless indicated otherwise, mass spectral data in Table 2 was collected using electrospray ionization in the positive ion mode. The HPLC method and retention time, along with mass spectral data are provided in Table 2 below. HPLC methods used are as follows:

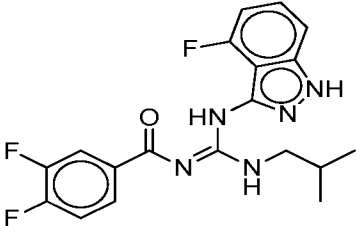
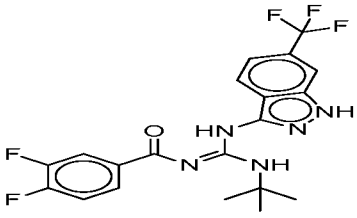
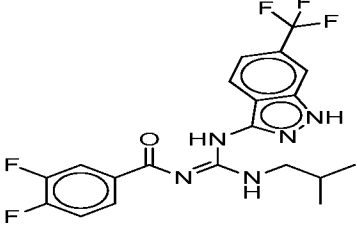
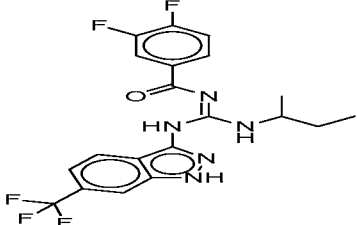
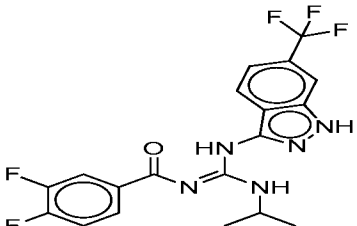
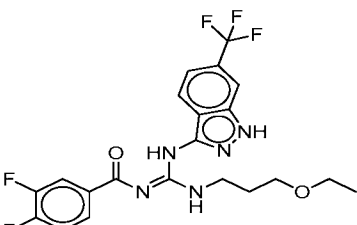
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Method A conditions were Waters Symmetry C-18 column, 4.6 x 150 mm, 3.5 micron, 23°C, 1.0 mL/min, 1 min 25% MeCN in H<sub>2</sub>O (0.1% TFA), 10 min gradient of 25%-95% MeCN in H<sub>2</sub>O (0.1% TFA), 95% MeCN in H<sub>2</sub>O (0.1% TFA) for 5 min, and then equilibration to 25% MeCN in H<sub>2</sub>O (0.1% TFA) over 2.0 min; Method B conditions were Agilent Zorbax C-18  
5 column, 4.6 x 50 mm, 1.8 micron, 23°C, 1.0 mL/min, 1 min 25% MeCN in H<sub>2</sub>O (0.1% TFA), 5 min gradient of 25%-95% MeCN in H<sub>2</sub>O (0.1% TFA), 1 min at 95% MeCN in H<sub>2</sub>O (0.1% TFA), and then equilibration to 25% MeCN in H<sub>2</sub>O (0.1% TFA) over 1.0 min; Method C conditions were Phenomenex Kinetex C18 (3.0 mm x 50 mm), 2.6 micron, 58°C, 1.5 mL/min, 4 min gradient 5% MeCN (0.1% TFA) in H<sub>2</sub>O (0.1% TFA) to 100% MeCN (0.1% TFA), 100%  
10 MeCN (0.1% TFA) for 0.5 min, and then equilibration to 5% MeCN (0.1% TFA) in H<sub>2</sub>O (0.1% TFA) over 1.5 min; Method D conditions were Phenomenex Kinetex C18 (3.0 mm x 50 mm), 2.6 micron, 40 °C, 1.5 mL/min, 4 min gradient 5% MeCN (0.1% TFA) in H<sub>2</sub>O (0.1% TFA) to 100% MeCN (0.1% TFA), 100% MeCN (0.1% TFA) for 0.5 min, and then equilibration to 5% MeCN (0.1% TFA) in H<sub>2</sub>O (0.1% TFA) over 1.5 min; Method E conditions were Waters  
15 Symmetry C18 (4.6 mm x 150 mm), 3.5 micron, 26 °C, 2.0 mL/min, 1 min 25% MeCN (0.05% TFA) in H<sub>2</sub>O (0.05% TFA), 7 min gradient of 25%-95% MeCN (0.05% TFA) in H<sub>2</sub>O (0.05% TFA), 95% MeCN (0.05% TFA) in H<sub>2</sub>O (0.05% TFA) for 2 min, and then equilibration to 25% MeCN (0.05% TFA) in H<sub>2</sub>O (0.05% TFA) over 2.0 min; and Method F conditions were Shim-pack XR-ODS, 2.2 micron, 40 °C, 1.0 mL/min, 10 min gradient 5% MeCN (0.1% TFA) in H<sub>2</sub>O  
20 (0.1% TFA) to 100% MeCN (0.1% TFA), 100% MeCN (0.1% TFA) for 1 min, and then equilibration to 5% MeCN (0.1% TFA) in H<sub>2</sub>O (0.1% TFA) over 1 min. The phrase “MeCN (0.05% TFA)” is art-recognized and refers to acetonitrile containing 0.05% wt/wt trifluoroacetic acid. The phrase “H<sub>2</sub>O (0.1% TFA)” is art-recognized and refers to water containing 0.1% wt/wt trifluoroacetic acid. The symbol “NA” indicates that no data was  
25 available.

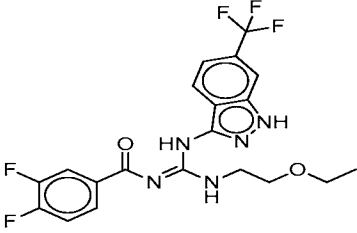
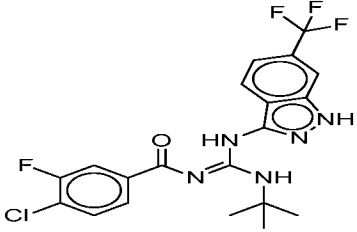
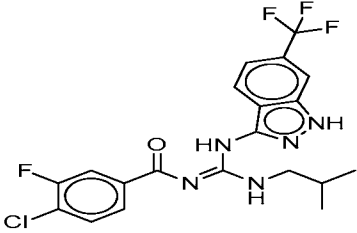
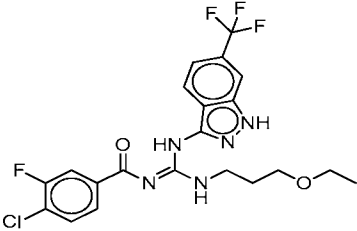
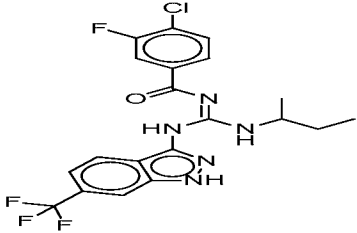
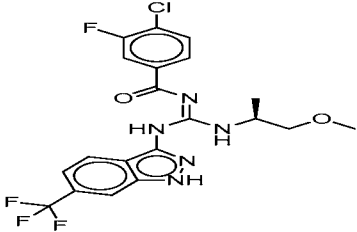
[00263] <sup>1</sup>H nuclear magnetic resonance data for exemplary compounds is provided in Table 3. The <sup>1</sup>H NMR data was taken using DMSO-d<sub>6</sub> as the solvent.

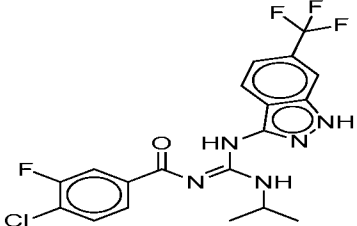
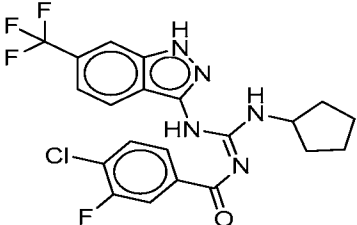
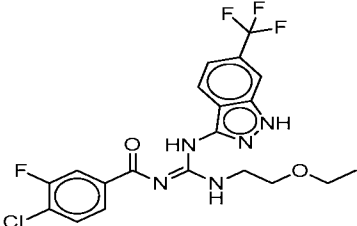
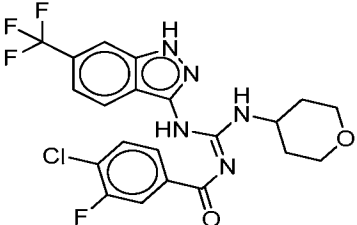
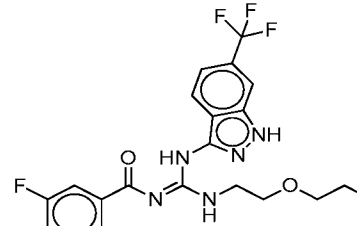
TABLE 2

| Compound No. | Chemical Structure                                                                  | Calculated MW (g/mol) | MS (m/z)                  | HPLC Method | HPLC Retention Time (min) |
|--------------|-------------------------------------------------------------------------------------|-----------------------|---------------------------|-------------|---------------------------|
| A-1          |    | 381.86                | 381.93, 383.89            | A           | 12.59                     |
| A-2          |   | 407.36                | 408.06                    | B           | 6.14                      |
| A-3          |  | 389.37                | 412.09 (Na <sup>+</sup> ) | B           | 7.21                      |
| A-4          |  | 389.37                | 390.12                    | B           | 6.07                      |
| A-5          |  | 389.37                | 412.15 (Na <sup>+</sup> ) | B           | 7.09                      |

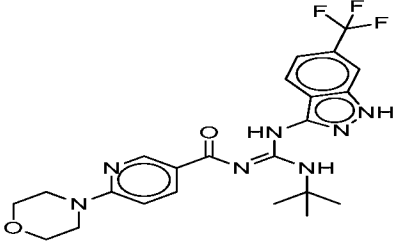
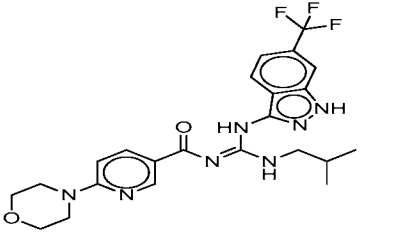
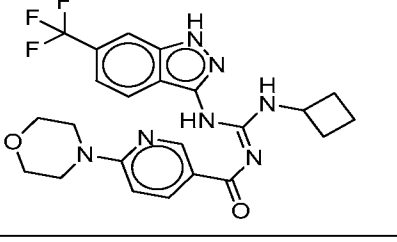
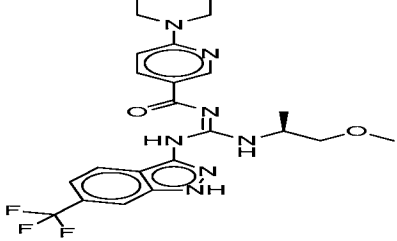
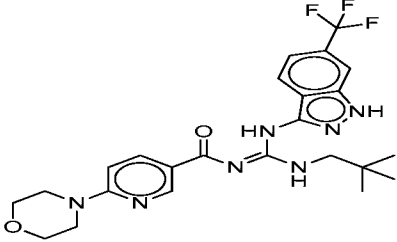
| Compound No. | Chemical Structure                                                                  | Calculated MW (g/mol) | MS (m/z) | HPLC Method | HPLC Retention Time (min) |
|--------------|-------------------------------------------------------------------------------------|-----------------------|----------|-------------|---------------------------|
| A-6          |    | 389.37                | 390.06   | B           | 6.71                      |
| A-7          |    | 439.38                | 462.05   | B           | 7.66                      |
| A-8          |   | 439.38                | 440.09   | B           | 6.94                      |
| A-9          |  | 439.38                | 440.09   | B           | 7.14                      |
| A-10         |  | 425.36                | 426.06   | B           | 6.85                      |
| A-11         |  | 469.41                | 470.11   | B           | 6.51                      |

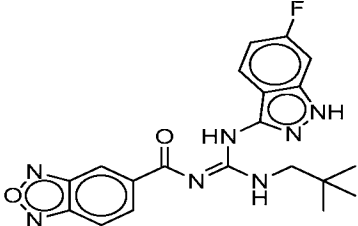
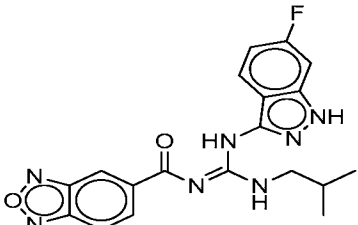
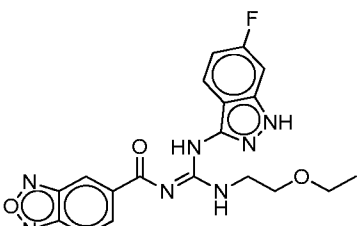
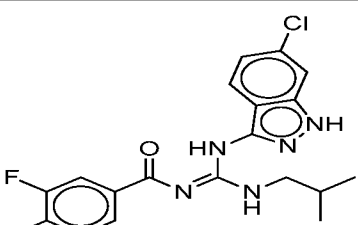
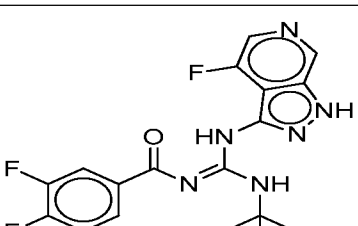
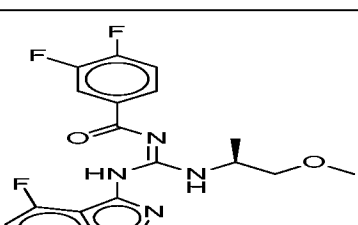
- 86 -

| Compound No. | Chemical Structure                                                                  | Calculated MW (g/mol) | MS (m/z) | HPLC Method | HPLC Retention Time (min) |
|--------------|-------------------------------------------------------------------------------------|-----------------------|----------|-------------|---------------------------|
| A-12         |    | 455.38                | 456.08   | B           | 6.24                      |
| A-13         |    | 455.84                | 478.04   | B           | 8.17                      |
| A-14         |  | 455.84                | 456.01   | B           | 7.56                      |
| A-15         |  | 485.86                | 486.03   | B           | 7.06                      |
| A-16         |  | 455.84                | 456.01   | B           | 7.68                      |
| A-17         |  | 471.84                | 472      | B           | 7.05                      |

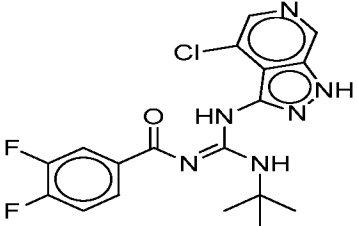
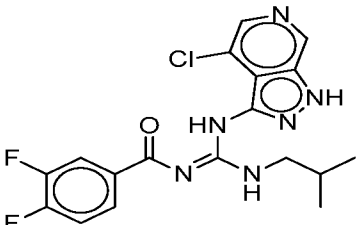
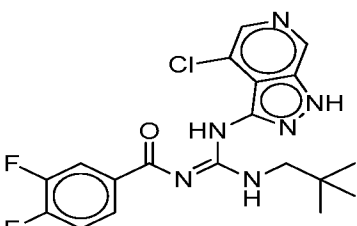
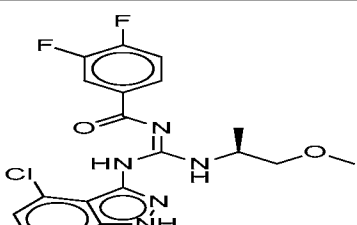
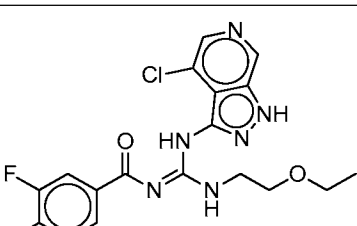
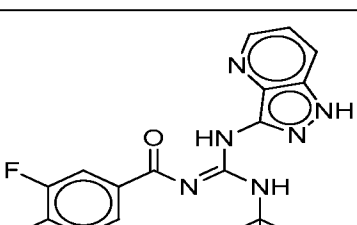
| Compound No. | Chemical Structure                                                                  | Calculated MW (g/mol) | MS (m/z) | HPLC Method | HPLC Retention Time (min) |
|--------------|-------------------------------------------------------------------------------------|-----------------------|----------|-------------|---------------------------|
| A-18         |    | 441.81                | 442.04   | B           | 7.38                      |
| A-19         |    | 467.85                | 468.03   | B           | 7.74                      |
| A-20         |  | 471.84                | 472      | B           | 6.79                      |
| A-21         |  | 483.85                | 484.02   | B           | 7.3                       |
| A-22         |  | 487.84                | 487.98   | B           | 5.68                      |

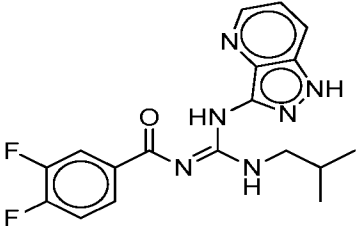
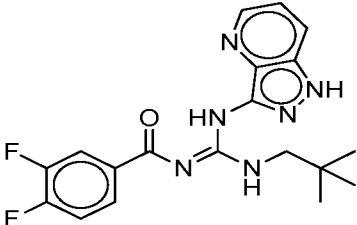
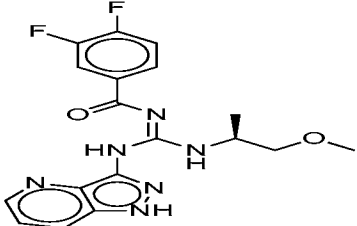
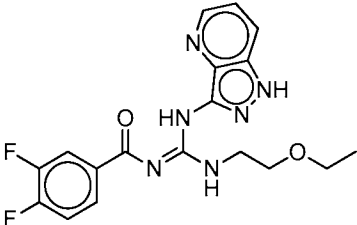
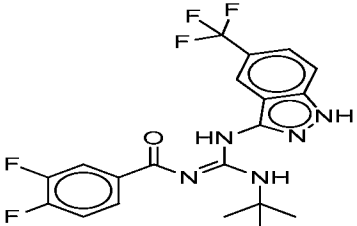
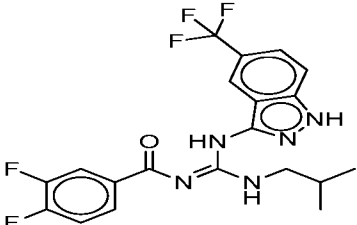
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| Compound No. | Chemical Structure                                                                  | Calculated MW (g/mol) | MS (m/z) | HPLC Method | HPLC Retention Time (min) |
|--------------|-------------------------------------------------------------------------------------|-----------------------|----------|-------------|---------------------------|
| A-23         |    | 489.49                | 490.13   | B           | 5.22                      |
| A-24         |    | 489.49                | 490.06   | B           | 4.95                      |
| A-25         |  | 487.48                | 488.05   | B           | 4.83                      |
| A-26         |  | 505.49                | 506.12   | B           | 4.64                      |
| A-27         |  | 503.52                | 504.1    | B           | 5.2                       |

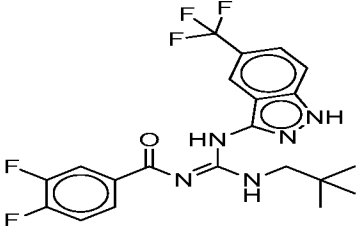
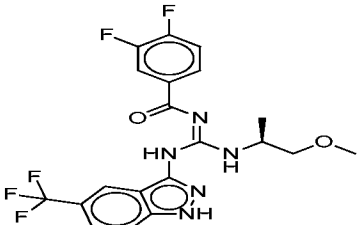
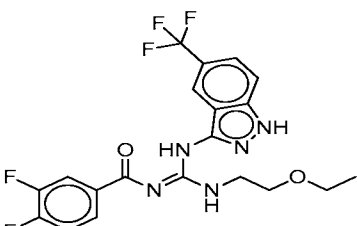
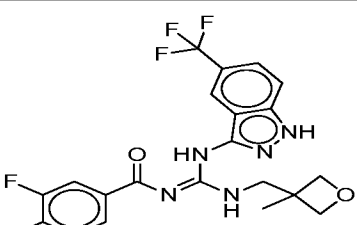
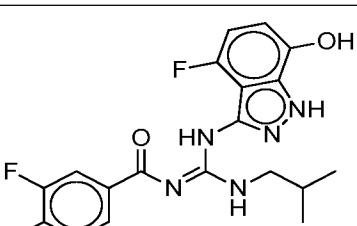
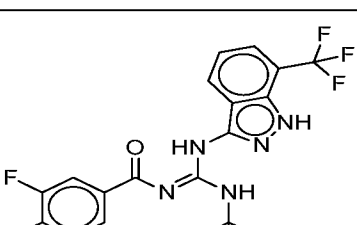
| Compound No. | Chemical Structure                                                                  | Calculated MW (g/mol) | MS (m/z) | HPLC Method | HPLC Retention Time (min) |
|--------------|-------------------------------------------------------------------------------------|-----------------------|----------|-------------|---------------------------|
| A-28         |    | 409.42                | 410.07   | B           | 7.09                      |
| A-29         |    | 395.39                | 396.04   | B           | 6.84                      |
| A-30         |   | 411.39                | 412.02   | B           | 6.12                      |
| A-31         |  | 405.83                | 404, 406 | E           | 7.58                      |
| A-32         |  | 390.36                | 413.07   | B           | 6.2                       |
| A-33         |  | 406.36                | 407.09   | B           | 5.17                      |

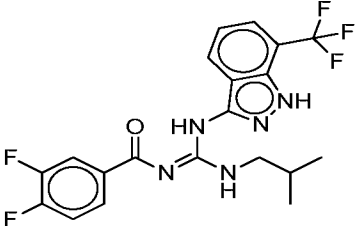
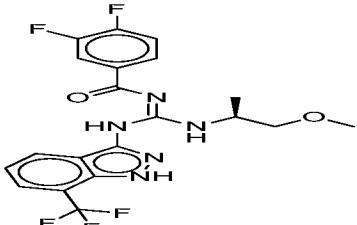
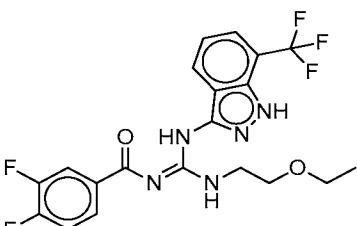
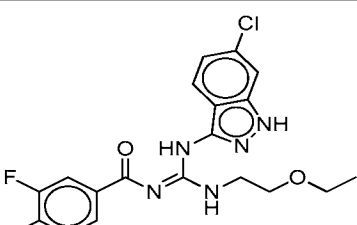
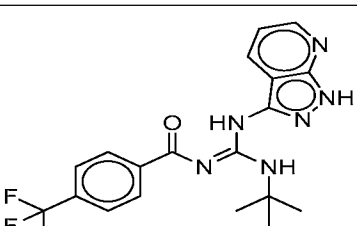
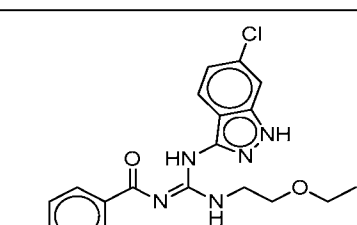
| Compound No. | Chemical Structure | Calculated MW (g/mol) | MS (m/z)   | HPLC Method | HPLC Retention Time (min) |
|--------------|--------------------|-----------------------|------------|-------------|---------------------------|
| A-34         |                    | 371.38                | 394 (M+Na) | E           | 8.525                     |
| A-35         |                    | 371.38                | 372        | E           | 6.535                     |
| A-36         |                    | 385.41                | 386        | E           | 6.977                     |
| A-37         |                    | 387.38                | 388        | E           | 5.902                     |
| A-38         |                    | 387.38                | 388        | E           | 5.546                     |
| A-39         |                    | 399.39                | 400        | E           | 6.139                     |

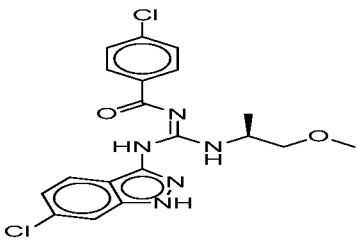
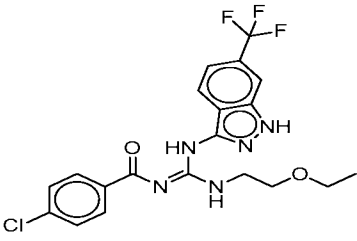
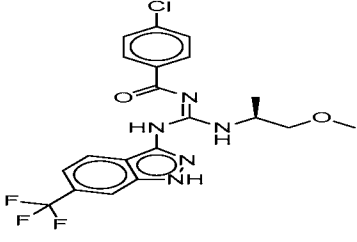
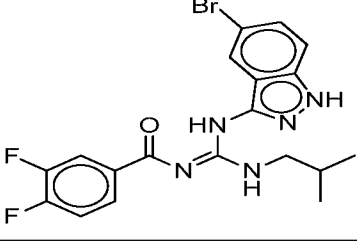
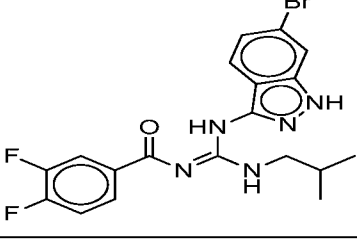
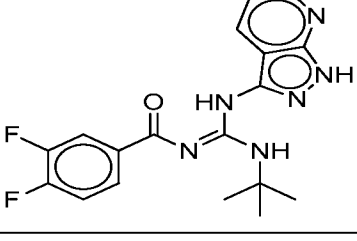
| Compound No. | Chemical Structure                                                                  | Calculated MW (g/mol) | MS (m/z) | HPLC Method | HPLC Retention Time (min) |
|--------------|-------------------------------------------------------------------------------------|-----------------------|----------|-------------|---------------------------|
| A-40         |    | 406.82                | 429.06   | B           | 7.84                      |
| A-41         |    | 406.82                | 429.06   | E           | 7.33                      |
| A-42         |   | 420.84                | 421.07   | E           | 7.76                      |
| A-43         |  | 422.82                | 423.02   | E           | 6.24                      |
| A-44         |  | 422.82                | 423.02   | E           | 5.89                      |
| A-45         |  | 372.37                | 395.13   | E           | 7.34                      |

| Compound No. | Chemical Structure                                                                  | Calculated MW (g/mol) | MS (m/z)           | HPLC Method | HPLC Retention Time (min) |
|--------------|-------------------------------------------------------------------------------------|-----------------------|--------------------|-------------|---------------------------|
| A-46         |    | 372.37                | 395.13             | E           | 5.69                      |
| A-47         |    | 386.4                 | 409.11             | E           | 6.2                       |
| A-48         |  | 388.37                | 411.06             | E           | 5.07                      |
| A-49         |  | 388.37                | 411.06             | E           | 4.83                      |
| A-50         |  | 439.38                | 466 (M-H negative) | E           | 9.174                     |
| A-51         |  | 439.38                | 440                | E           | 7.616                     |

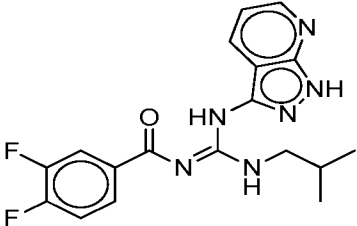
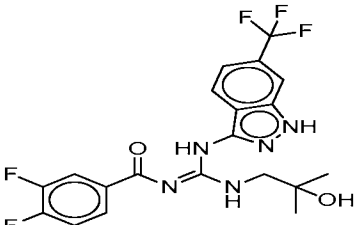
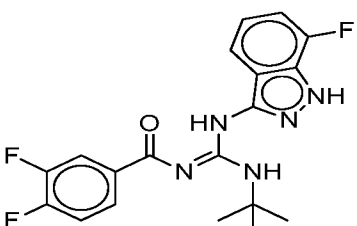
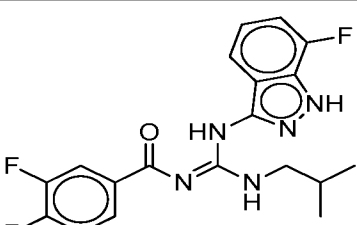
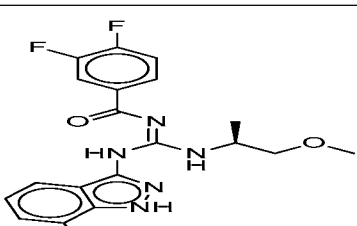
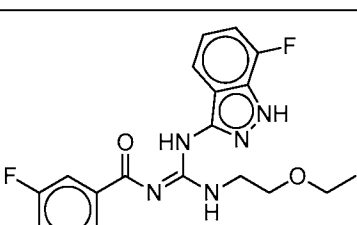
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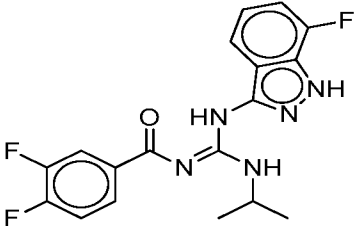
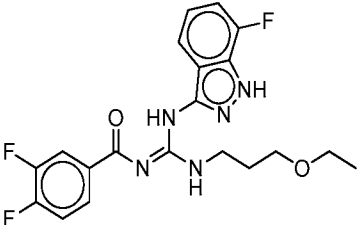
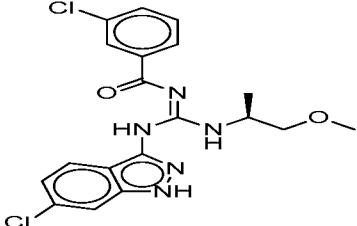
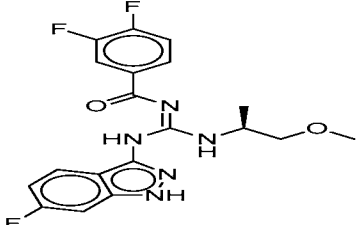
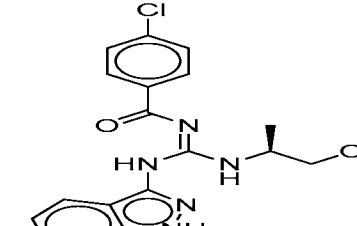
| Compound No. | Chemical Structure                                                                  | Calculated MW (g/mol) | MS (m/z) | HPLC Method | HPLC Retention Time (min) |
|--------------|-------------------------------------------------------------------------------------|-----------------------|----------|-------------|---------------------------|
| A-52         |    | 453.41                | 454      | E           | 8.007                     |
| A-53         |    | 455.38                | 456      | E           | 7.061                     |
| A-54         |   | 455.38                | 456      | E           | 6.631                     |
| A-55         |  | 467.39                | 468      | E           | 7.246                     |
| A-56         |  | 405.37                | 428.03   | E           | 6.83                      |
| A-57         |  | 439.38                | 462.02   | E           | 9.26                      |

| Compound No. | Chemical Structure                                                                  | Calculated MW (g/mol) | MS (m/z)   | HPLC Method | HPLC Retention Time (min) |
|--------------|-------------------------------------------------------------------------------------|-----------------------|------------|-------------|---------------------------|
| A-58         |    | 439.38                | 440.05     | E           | 7.75                      |
| A-59         |    | 455.38                | 456.04     | E           | 7.17                      |
| A-60         |   | 455.38                | 456.04     | E           | 6.74                      |
| A-61         |  | 421.83                | N/A        | E           | 6.34                      |
| A-62         |  | 404.39                | 405.4      | D           | 2.87                      |
| A-63         |  | 420.29                | 422, 420.0 | E           | 6                         |

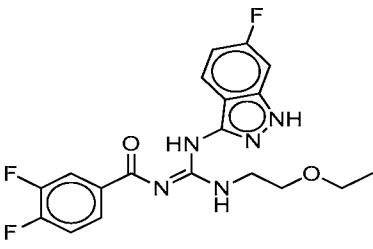
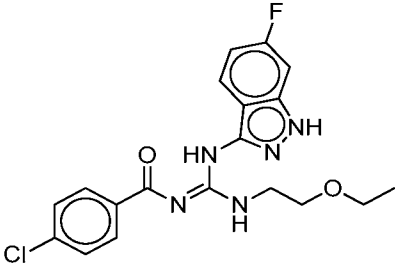
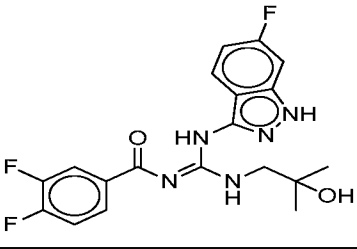
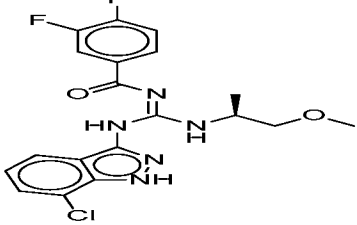
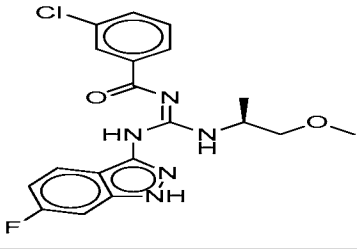
| Compound No. | Chemical Structure                                                                  | Calculated MW (g/mol) | MS (m/z)       | HPLC Method | HPLC Retention Time (min) |
|--------------|-------------------------------------------------------------------------------------|-----------------------|----------------|-------------|---------------------------|
| A-64         |    | 420.29                | 421.99, 419.99 | E           | 6.32                      |
| A-65         |    | 453.85                | 454.03         | E           | 6.34                      |
| A-66         |  | 453.85                | 454.03         | N/A         | N/A                       |
| A-67         |  | 450.28                | 450, 448       | E           | 7.41                      |
| A-68         |  | 450.28                | N/A            | E           | 7.54                      |
| A-69         |  | 372.37                | 373.2          | D           | 2.67                      |

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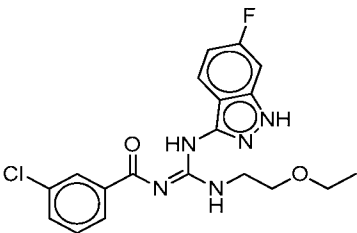
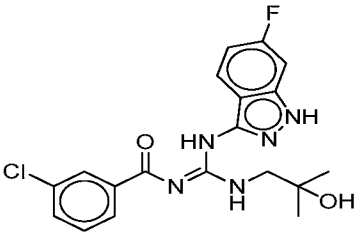
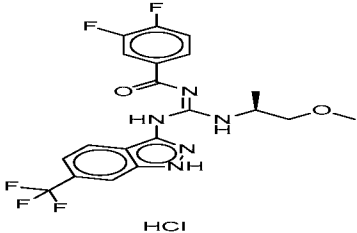
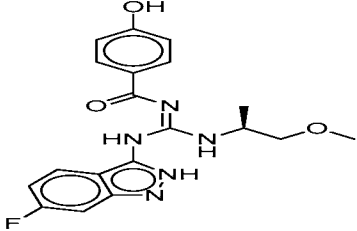
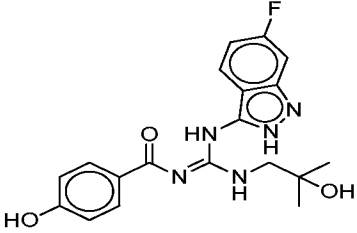
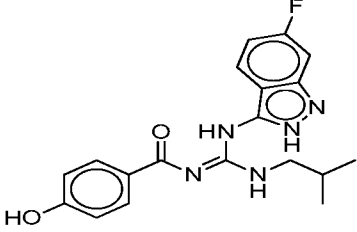
| Compound No. | Chemical Structure                                                                  | Calculated MW (g/mol) | MS (m/z) | HPLC Method | HPLC Retention Time (min) |
|--------------|-------------------------------------------------------------------------------------|-----------------------|----------|-------------|---------------------------|
| A-70         |    | 372.37                | 373.2    | D           | 2.16                      |
| A-71         |    | 455.38                | 456      | E           | 5.762                     |
| A-72         |   | 389.37                | 390.06   | E           | 8.82                      |
| A-73         |  | 389.37                | 390.06   | E           | 7.14                      |
| A-74         |  | 405.37                | 406.05   | E           | 6.47                      |
| A-75         |  | 405.37                | 406.05   | E           | 6.06                      |

| Compound No. | Chemical Structure                                                                  | Calculated MW (g/mol) | MS (m/z) | HPLC Method | HPLC Retention Time (min) |
|--------------|-------------------------------------------------------------------------------------|-----------------------|----------|-------------|---------------------------|
| A-76         |    | 375.35                | 376.02   | E           | 6.9                       |
| A-77         |    | 419.4                 | 420.03   | E           | 6.4                       |
| A-78         |  | 420.29                | N/A      | N/A         | N/A                       |
| A-79         |  | 405.37                | N/A      | E           | 4.96                      |
| A-80         |  | 403.84                | 404      | E           | 4.81                      |

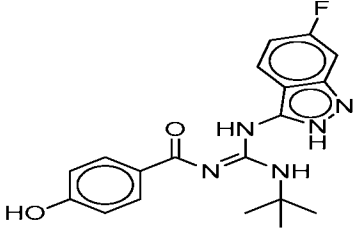
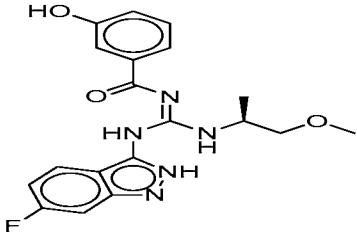
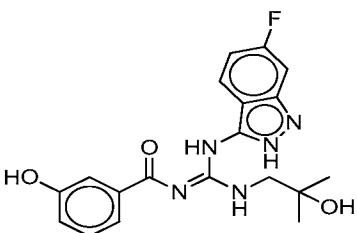
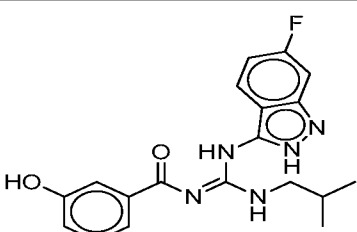
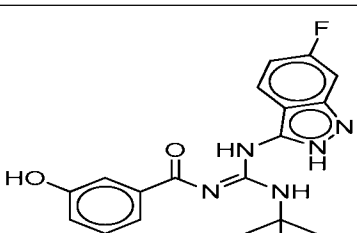
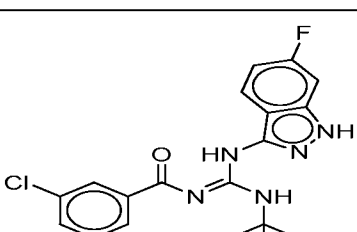
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| Compound No. | Chemical Structure                                                                  | Calculated MW (g/mol) | MS (m/z) | HPLC Method | HPLC Retention Time (min) |
|--------------|-------------------------------------------------------------------------------------|-----------------------|----------|-------------|---------------------------|
| A-81         |    | 405.37                | N/A      | E           | 4.76                      |
| A-82         |   | 403.84                | N/A      | E           | 4.73                      |
| A-83         |  | 405.37                | N/A      | E           | 5.01                      |
| A-84         |  | 421.83                | N/A      | E           | 7                         |
| A-85         |  | 403.84                | 404.1    | E           | 4.9                       |

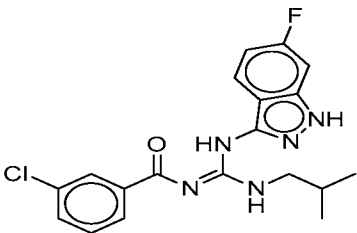
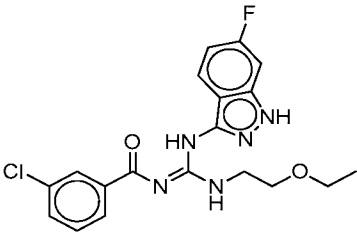
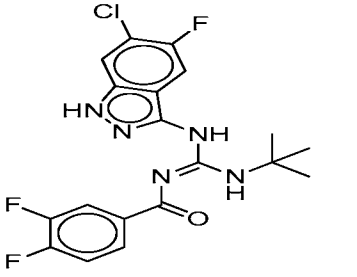
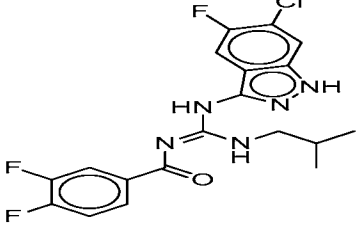
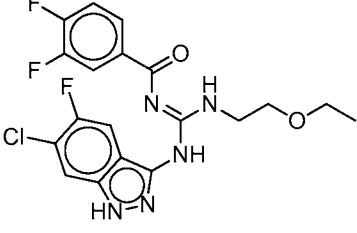
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| Compound No. | Chemical Structure                                                                  | Calculated MW (g/mol) | MS (m/z)     | HPLC Method | HPLC Retention Time (min) |
|--------------|-------------------------------------------------------------------------------------|-----------------------|--------------|-------------|---------------------------|
| A-86         |    | 403.84                | N/A          | E           | 5.85                      |
| A-87         |    | 403.84                | N/A          | E           | 4.75                      |
| A-88         |  | 491.84                | N/A          | N/A         | N/A                       |
| A-89         |  | 385.39                | 386.09       | E           | 4.06                      |
| A-90         |  | 385.39                | 384.21 (M-1) | E           | 3.76                      |
| A-91         |  | 369.39                | 368.15 (M-1) | E           | 4.38                      |

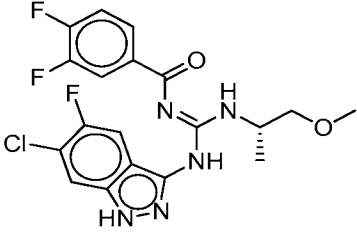
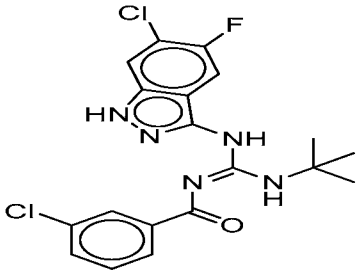
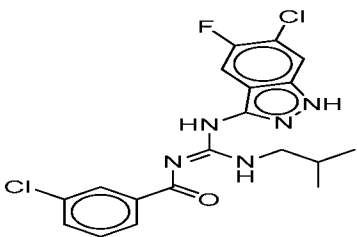
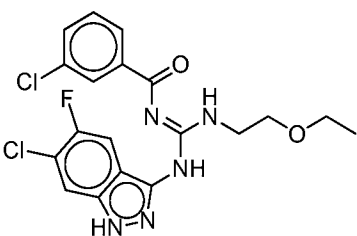
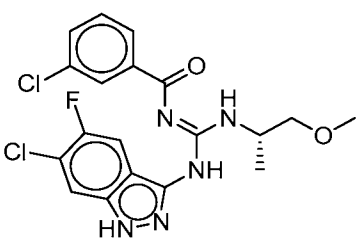
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| Compound No. | Chemical Structure                                                                  | Calculated MW (g/mol) | MS (m/z)     | HPLC Method | HPLC Retention Time (min) |
|--------------|-------------------------------------------------------------------------------------|-----------------------|--------------|-------------|---------------------------|
| A-92         |    | 369.39                | 368.15 (M-1) | E           | 5.54                      |
| A-93         |    | 385.39                | 384.14 (M-1) | E           | 4.09                      |
| A-94         |   | 385.39                | 384.27 (M-1) | E           | 3.73                      |
| A-95         |  | 369.39                | 368.15 (M-1) | E           | 4.45                      |
| A-96         |  | 369.39                | 368.21 (M-1) | E           | 6.12                      |
| A-97         |  | 387.84                | 388.1        | F           | 2.23                      |

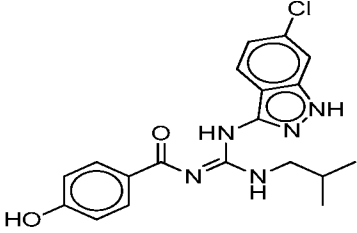
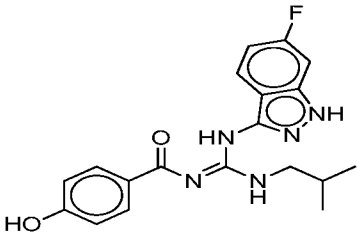
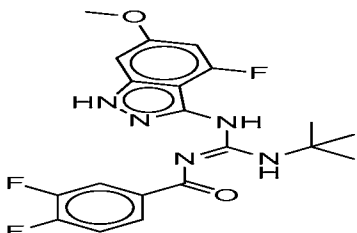
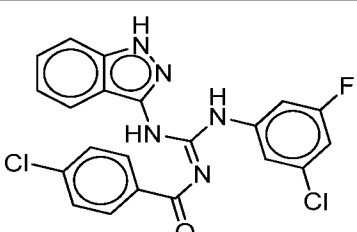
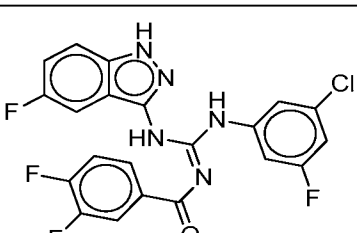
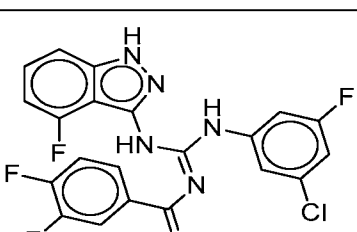
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| Compound No. | Chemical Structure                                                                  | Calculated MW (g/mol) | MS (m/z) | HPLC Method | HPLC Retention Time (min) |
|--------------|-------------------------------------------------------------------------------------|-----------------------|----------|-------------|---------------------------|
| A-98         |    | 387.84                | 388      | F           | 1.97                      |
| A-99         |    | 403.84                | 404      | F           | 2.28                      |
| A-100        |  | 423.82                | 424/426  | E           | 9.582                     |
| A-101        |  | 423.82                | 424/426  | E           | 7.745                     |
| A-102        |  | 439.82                | 440/442  | E           | 6.683                     |

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| Compound No. | Chemical Structure                                                                  | Calculated MW (g/mol) | MS (m/z) | HPLC Method | HPLC Retention Time (min) |
|--------------|-------------------------------------------------------------------------------------|-----------------------|----------|-------------|---------------------------|
| A-103        |    | 439.82                | 440/442  | E           | 7.161                     |
| A-104        |   | 422.28                | N/A      | E           | 9.895                     |
| A-105        |  | 422.28                | 422/424  | E           | 7.59                      |
| A-106        |  | 438.28                | 438/440  | E           | 6.502                     |
| A-107        |  | 438.28                | 438/440  | E           | 6.979                     |

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| Compound No. | Chemical Structure                                                                  | Calculated MW (g/mol) | MS (m/z)          | HPLC Method | HPLC Retention Time (min) |
|--------------|-------------------------------------------------------------------------------------|-----------------------|-------------------|-------------|---------------------------|
| A-108        |    | 385.85                | 385.6             | F           | 2.49                      |
| A-109        |    | 369.39                | 369.9             | F           | 2.6                       |
| A-110        |   | 419.4                 | 420.1             | D           | 2.98                      |
| A-111        |  | 442.27                | 441.80,<br>443.80 | A           | 16.8                      |
| A-112        |  | 461.8                 | 461.99            | B           | 7.99                      |
| A-113        |  | 461.8                 | 461.99            | B           | 7.79                      |

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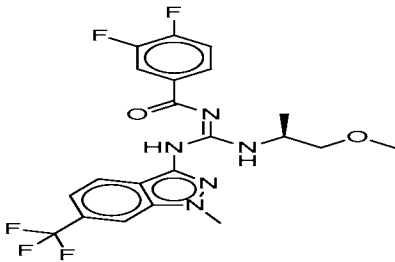
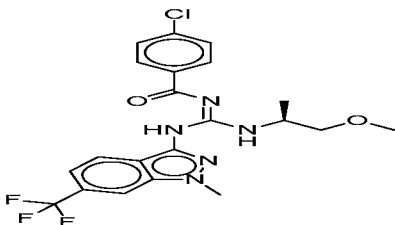
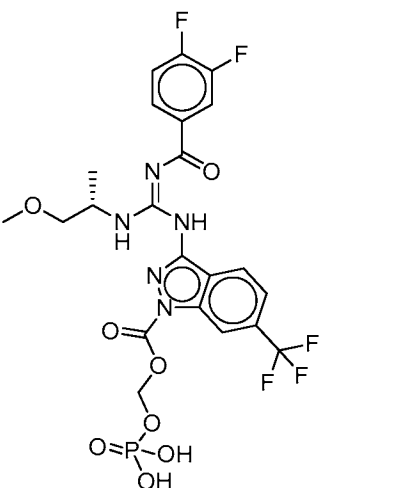
| Compound No. | Chemical Structure                                                                  | Calculated MW (g/mol) | MS (m/z) | HPLC Method | HPLC Retention Time (min) |
|--------------|-------------------------------------------------------------------------------------|-----------------------|----------|-------------|---------------------------|
| A-114        |    | 469.41                | N/A      | E           | 8.14                      |
| A-115        |    | 467.87                | N/A      | E           | 7.63                      |
| A-116        |  | N/A                   | N/A      | N/A         | N/A                       |

TABLE 3

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| Compound No. | <sup>1</sup> H NMR Resonance Data (δ)                                                                                                                           |
|--------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| A-1          | 13.59 (s, 1H), 12.85 (s, 1H), 9.01 (s, 1H), 8.15 (m, 2H), 7.66 (m, 1H), 7.53-7.44 (m, 4H), 7.19 (m, 1H), 2.42 (m, 2H), 2.22 (m, 2H), 1.92 (m, 2H), 1.68 (s, 3H) |
| A-2          | 13.40 (s, 1H), 13.28 (s, 1H), 8.61 (d, 1H), 8.02 (m, 2H), 7.85 (d, 1H), 7.72 (s, 2H), 7.68 - 7.30 (m, 4H), 4.47 (m, 1H), 1.32 (d, 6H)                           |

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| Compound No. | <sup>1</sup> H NMR Resonance Data (δ)                                                                                                                       |
|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|
| A-3          | 13.47 (s), 13.02 (s, 1H), 8.90 (s, 1H), 8.00 (m, 2H), 7.55 (m, 2H), 7.36 (m, 2H), 1.58 (s, 9H)                                                              |
| A-4          | 13.21 (s, 1H), 12.99 (s, 1H), 8.80 (t, 1H), 8.00 (m, 2H), 7.52 (m, 2H), 7.35 (m, 2H), 3.46 (d, 2H), 1.96 (m, 1H), 0.98 (d, 6H)                              |
| A-5          | 13.63 (s, 1H), 13.17 (s, 1H), 9.01 (s, 1H), 8.00 (m, 2H), 7.53 (q, 1H), 7.40 (m, 1H), 7.29 (m, 1H), 6.90 (t, 1H), 1.58 (s, 9H).                             |
| A-6          | 13.52 (s, 1H), 13.13 (s, 1H), 8.96 (t, 1H), 8.02 (m, 2H), 7.43 (m, 2H), 7.31 (m, 1H), 6.91 (m, 1H), 3.50 (m, 2H), 1.98 (m, 1H), 1.00 (d, 6H)                |
| A-7          | 13.72 (s, 1H), 13.36 (s, 1H), 8.86 (s, 1H), 7.99 (m, 2H), 7.87 (m, 2H), 7.50 (m, 2H), 1.58 (s, 9H)                                                          |
| A-8          | 13.44 (s, 1H), 13.31 (s, 1H), 8.80 (t, 1H), 8.01 (m, 2H), 7.90 (m, 2H), 7.48 (m, 2H), 13.48 (m, 2H), 1.98 (m, 1H), 0.98 (d, 6H)                             |
| A-9          | 13.48 (s, 1H), 13.27 (s, 1H), 8.61 (m, 1H), 8.03 (m, 2H), 7.90 (m, 2H), 7.48 (m, 2H), 4.35 (m, 1H), 1.62 (m, 2H), 1.27 (m, 3H), 0.96 (m, 3H)                |
| A-10         | 13.44 (s, 1H), 13.28 (s, 1H), 8.60 (d, (1H), 8.02 (m, 2H), 7.88 (m, 2H), 7.48 (m, 2H), 4.46 (m, 1H), 4.05 (bs, 1H), 3.15 (s, 3H), 1.30 (d, 6H)              |
| A-11         | 13.40 (s, 1H), 13.24 (s, 1H), 8.75 (t, 1H), 8.03 (m, 2H), 7.88 (m, 2H), 7.47 (m, 2H), 3.70 (m, 2H), 3.43 (m, 5H), 1.84 (m, 2H), 1.09 (m, 3H)                |
| A-12         | 13.47 (s, 1H), 13.33 (s, 1H), 8.95 (s, 1H), 8.00 (m, 4H), 7.50 (m, 2H), 3.80 (s, 3H), 3.60 (m, 5H), 1.20 (m, 4H)                                            |
| A-13         | 13.67 (s, 1H), 13.37 (s, 1H), 8.89 (s, 1H), 7.92 (m, 4H), 7.70 (m, 1H), 7.44 (m, 1H), 1.59 (s, 9H)                                                          |
| A-14         | 13.41 (s, 1H), 13.30 (bs, 1H), 8.81 (t, 1H), 8.00 (m, 2H), 7.89 (m, 2H), 7.67 (m, 1H), 7.43 (m, 1H), 3.48 (m, 2H), 1.96 (m, 1H), 0.99 (m, 6H)               |
| A-15         | 13.40 (s, 1H), 13.22 (bs, 1H), 8.74 (s, 1H), 8.00 (m, 2H), 7.84 (m, 2H), 7.61 (m, 1H), 7.42 (m, 1H), 3.68 (m, 2H), 3.42 (m, 5H), 1.84 (m, 2H), 1.09 (m, 3H) |
| A-16         | 13.43 (s, 1H), 13.28 (bs, 1H), 8.62 (d, 1H), 8.00 (m, 2H), 7.88 (m, 2H), 7.64 (m, 1H), 7.43 (m, 1H), 4.33 (m, 1H), 1.62 (m, 2H), 1.27 (m, 3H), 0.95 (m, 3H) |
| A-17         | 13.48 (s, 1H), 13.32 (bs, 1H), 8.82 (d, 1H), 8.00 (m, 2H), 7.90 (m, 2H), 7.64 (m, 1H), 7.42 (m, 1H), 4.40 (m, 1H), 3.50 (m, 2H), 3.30 (s, 3H), 1.27 (d, 3H) |
| A-18         | 13.42 (s, 1H), 13.29 (bs, 1H), 8.61 (d, 1H), 8.00 (m, 2H), 7.90 (m, 2H), 7.68 (m, 1H), 7.46 (m, 1H), 4.47 (m, 1H), 1.30 (d, 6H)                             |
| A-19         | 13.41 (s, 1H), 13.28 (bs, 1H), 8.80 (d, 1H), 8.00 (m, 2H), 7.88 (m, 2H), 7.66 (m, 1H), 7.43 (m, 1H), 4.60 (m, 1H), 2.08 (m, 2H), 1.63 (m, 6H)               |
| A-20         | 13.41 (s, 1H), 13.32 (s, 1H), 8.93 (t, 1H), 8.01 (m, 2H), 7.89 (m, 2H), 7.64 (m, 1H), 7.44 (m, 1H), 3.80 (m, 2H), 3.63 (m, 2H), 3.50 (m, 2H), 1.15 (m, 3H)  |

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| Compound No. | <sup>1</sup> H NMR Resonance Data (δ)                                                                                                                                                  |
|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| A-21         | 13.40 (s, 1H), 13.30 (bs, 1H), 8.75 (d, 1H), 7.99 (m, 2H), 7.89 (m, 2H), 7.64 (m, 1H), 7.42 (m, 1H), 4.39 (m, 1H), 3.88 (m, 2H), 3.50 (m, 2H), 2.02 (m, 2H), 1.58 (m, 2H)              |
| A-22         | 13.40 (s, 1H), 13.30 (s, 1H), 8.91 (t, 1H), 8.01 (m, 2H), 7.88 (m, 3H), 7.67 (m, 1H), 7.47 (m, 1H), 4.60 (m, 1H), 3.80 (m, 2H), 3.68 (m, 2H), 3.52 (m, 4H)                             |
| A-28         | 13.38 (s, 1H), 13.02 (s, 1H), 9.10 (t, 1H), 8.69 (s, 1H), 8.30 (d, 1H), 8.09 (d, 1H), 7.73 (m, 1H), 7.30 (m, 1H), 7.08 (m, 1H), 3.56 (m, 2H), 1.01 (s, 9H)                             |
| A-29         | 13.28 (s, 1H), 12.99 (s, 1H), 8.99 (t, 1H), 8.69 (s, 1H), 8.30 (m, 1H), 8.08 (m, 1H), 7.72 (m, 1H), 7.32 (m, 1H), 7.07 (m, 1H), 3.53 (m, 2H), 1.99 (m, 1H), 1.00 (d, 6H)               |
| A-30         | 13.25 (s, 1H), 12.96 (s, 1H), 9.05 (m, 1H), 8.68 (m, 1H), 8.25 (m, 1H), 8.02 (m, 1H), 7.68 (m, 1H), 7.28 (m, 1H), 7.05 (m, 1H), 3.83 (m, 2H), 3.65 (m, 2H), 3.52 (m, 2H), 1.16 (t, 3H) |
| A-31         | 13.38 (s, 1H), 12.5 (br s, 1H), 8.85 (tr, 1H), 8.0 (m, 2H), 7.68 (d, 1H), 7.59 (d, 1H), 7.48 (dd, 1H), 7.19 (dd, 1H), 3.48 (t, 2H), 1.96 (m, 1H), 0.98 (d, 6H)                         |
| A-32         | 13.79 (s, 1H), 13.74 (s, 1H), 8.82 (m, 2H), 8.20 (s, 1H), 7.99 (m, 2H), 7.54 (m, 1H), 1.58 (s, 9H)                                                                                     |
| A-33         | 13.72 (bs, 1H), 13.60 (s, 1H), 8.80 (m, 2H), 8.20 (s, 1H), 8.02 (m, 2H), 7.49 (m, 1H), 4.61 (m, 1H), 3.50 (s, 2H), 3.30 (s, 3H), 1.28 (m, 3H)                                          |
| A-34         | 13.65 (s, 1H), 12.93 (s, 1H), 9.27 (s, 1H), 8.04 (m, 2H), 7.68 (d, 1H), 7.55 (m, 3H), 7.22 (t, 1H), 1.61 (s, 9H)                                                                       |
| A-35         | 13.43 (s, 1H), 12.90 (s, 1H), 8.98 (t, 1H), 8.10 (m, 2H), 7.70 (d, 1H), 7.54 (m, 3H), 7.23 (t, 1H), 3.53 (t, 2H), 1.99 (m, 1H), 1.01 (d, 6H)                                           |
| A-36         | 13.54 (s, 1H), 12.95 (s, 1H), 9.11 (t, 1H), 8.08 (m, 2H), 7.71 (d, 1H), 7.54 (m, 3H), 7.23 (t, 1H), 3.55 (d, 2H), 1.03 (s, 9H)                                                         |
| A-37         | 13.49 (s, 1H), 12.91 (s, 1H), 9.00 (m, 1H), 8.10 (m, 2H), 7.69 (d, 1H), 7.51 (m, 3H), 7.23 (m, 1H), 4.65 (br s, 1H), 3.55 (m, 2H), 3.37 (s, 3H), 1.33 (d, 3H)                          |
| A-38         | 13.45 (s, 1H), 12.90 (s, 1H), 9.08 (m, 1H), 8.10 (m, 2H), 7.69 (d, 1H), 7.50 (m, 3H), 7.22 (t, 1H), 3.84 (m, 2H), 3.65 (m, 2H), 3.55 (q, 2H), 1.18 (t, 3H)                             |
| A-39         | 13.50 (s, 1H), 12.94 (s, 1H), 9.12 (t, 1H), 8.10 (m, 2H), 7.70 (d, 1H), 7.54 (m, 3H), 7.23 (t, 1H), 4.54 (d, 2H), 4.30 (d, 2H), 4.03 (d, 2H), 1.37 (s, 3H)                             |
| A-40         | 13.80 (m, 2H), 9.07 (s, 1H), 8.95 (s, 1H), 8.24 (s, 1H), 7.99 (m, 2H), 7.52 (m, 1H), 1.58 (s, 9H)                                                                                      |
| A-41         | 13.78 (s, 1H), 13.55 (s, 1H), 8.90 (m, 2H), 8.23 (s, 1H), 8.00 (m, 2H), 7.47 (m, 1H), 3.46 (m, 2H), 1.98 (m, 1H), 0.96 (d, 6H)                                                         |
| A-42         | 13.80 (bs, 1H), 13.66 (s, 1H), 9.06 (t, 1H), 8.95 (s, 1H), 8.24 (s, 1H), 8.00 (m, 2H), 7.48 (m, 1H), 3.51 (d, 2H), 1.00 (s, 9H)                                                        |

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| Compound No. | <sup>1</sup> H NMR Resonance Data (δ)                                                                                                                                    |
|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| A-43         | 13.80 (bs, 1H), 13.60 (s, 1H), 9.00 (m, 2H), 8.22 (s, 1H), 8.01 (m, 2H), 7.48 (m, 1H), 4.60 (m, 1H), 3.51 (m, 2H), 3.30 (s, 3H), 1.27 (d, 3H)                            |
| A-44         | 13.78 (bs, 1H), 13.59 (s, 1H), 9.05 (s, 1H), 8.97 (s, 1H), 8.24 (s, 1H), 8.02 (m, 2H), 7.46 (m, 1H), 3.80 (m, 2H), 3.62 (m, 2H), 3.50 (m, 2H), 1.15 (m, 3H)              |
| A-45         | 13.61 (s, 1H), 13.09 (bs, 1H), 9.00 (s, 1H), 8.52 (s, 1H), 8.00 (m, 3H), 7.51 (m, 2H), 1.59 (s, 9H)                                                                      |
| A-46         | 13.48 (s, 1H), 13.04 (bs, 1H), 9.00 (t, 1H), 8.52 (s, 1H), 8.02 (m, 3H), 7.49 (m, 2H), 3.51 (m, 2H), 1.98 (m, 1H), 0.98 (d, 6H)                                          |
| A-47         | 13.53 (s, 1H), 13.10 (s, 1H), 9.07 (t, 1H), 8.53 (s, 1H), 8.03 (m, 3H), 7.49 (m, 2H), 3.53 (d, 2H), 1.00 (s, 9H)                                                         |
| A-48         | 13.50 (s, 1H), 13.08 (s, 1H), 9.02 (d, 1H), 8.53 (s, 1H), 8.02 (m, 3H), 7.49 (m, 2H), 4.61 (m, 1H), 3.52 (d, 2H), 3.33 (s, 3H), 1.30 (d, 3H)                             |
| A-49         | 13.47 (s, 1H), 13.04 (bs, 1H), 9.08 (m, 1H), 8.53 (s, 1H), 8.03 (m, 3H), 7.48 (m, 2H), 3.81 (m, 2H), 3.62 (m, 2H), 3.52 (m, 2H), 1.13 (m, 3H)                            |
| A-50         | 13.60 (s, 1H), 13.32 (br s, 1H), 8.92 (s, 1H), 8.02 (m, 3H), 7.74 (m, 2H), 7.56 (q, 1H), 1.61 (s, 9H)                                                                    |
| A-51         | 13.33 (br s, 2H), 8.86 (m, 1H), 8.05 (m, 3H), 7.75 (m, 2H), 7.54 (m, 1H), 3.51 (t, 2H), 2.00 (m, 1H), 1.00 (d, 6H)                                                       |
| A-52         | 13.43 (s, 1H), 13.38 (br s, 1H), 8.99 (t, 1H), 8.07 (m, 3H), 7.75 (m, 2H), 7.53 (m, 1H), 3.54 (d, 2H), 1.03 (s, 9)                                                       |
| A-53         | 13.40 (s, 1H), 13.33 (br s, 1H), 8.88 (b, 1H), 8.07 (m, 3H), 7.75 (m, 2H), 7.52 (m, 1H), 4.63 (m, 1H), 3.53 (m, 2H), 3.36 (s, 3H), 1.32 (d, 3H)                          |
| A-54         | 13.36 (br s, 2H), 8.98 (m, 1H), 8.08 (m, 3H), 7.75 (m, 2H), 7.51 (q, 1H), 3.82 (m, 2H), 3.64 (m, 2H), 3.55 (m, 2H), 1.18 (t, 3H)                                         |
| A-55         | 13.35 (br s, 2H), 8.99 (m, 1H), 8.09 (m, 3H), 7.75 (m, 2H), 7.53 (q, 1H), 4.54 (m, 2H), 4.30 (m, 2H), 3.94 (m, 2H), 1.37 (s, 3H)                                         |
| A-56         | 13.42 (s, 1H), 13.27 (1H, s), 10.28 (s, 1H), 8.96 (t, 1H), 8.02 (m, 2H), 7.50 dd, 1H), 6.6 (m, 2H), 3.49 (t, 2H), 1.98 (m, 1H), 0.97 (d, 6H)                             |
| A-57         | 13.71 (s, 1H), 13.44 (s, 1H), 8.85 (s, 1H), 8.00 (m, 3H), 7.86 (d, 1H), 7.54 (m, 1H), 7.35 (m, 1H), 1.58 (s, 9H)                                                         |
| A-58         | 13.43 (m, 2H), 8.78 (t, 1H), 8.01 (m, 3H), 7.83 (m, 1H), 7.49 (m, 1H), 7.35 (m, 1H), 3.50 (m, 2H), 1.97 (m, 1H), 0.96 (d, 6H)                                            |
| A-59         | 13.52 (s, 1H), 13.23 (s, 1H), 8.82 (d, 1H), 8.00 (m, 3H), 7.83 (m, 1H), 7.47 (m, 1H), 7.33 (m, 1H), 4.41 (m, 1H), 3.50 (m, 2H), 3.30 (s, 3H), 3.14 (m, 2H), 1.29 (d, 3H) |

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| Compound No. | <sup>1</sup> H NMR Resonance Data (δ)                                                                                                                               |
|--------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| A-60         | 13.42 (m, 2H), 8.84 (m, 1H), 8.00 (m, 3H), 7.83 (m, 1H), 7.49 (m, 1H), 7.35 (m, 1H), 3.81 (m, 2H), 3.62 (m, 2H), 3.49 (m, 2H), 1.17 (t, 3H)                         |
| A-65         | 13.58 (s, 1H), 13.31 (s, 1H), 8.88 (br s 1H), 8.18 (d, 2H), 7.9 (m, 2H), 7.48 (m, 2H), 3.8 (m, 2H), 3.6 (m, 2H), 3.5 (q, 2H), 1.15 (t, 3H)                          |
| A-68         | 13.39 (s, 1H), 12.99 (s, 1H), 8.84 (s, 1H), 8.02 (m, 3H), 7.75 (d, 1H), 7.62 (d, 1H), 7.50 (dd, 1H), 7.31 (dd, 1H), 3.49 (t, 2H), 1.97 (m, 2H), 0.98 (d, 3H)        |
| A-71         | 13.63 (s, 1H), 13.41 (s, 1H), 9.07 (s, 1H), 8.08 (m, 2H), 7.94 (m, 2H), 7.54 (m, 2H), 4.85 (s, 1H), 3.65 (d, 2H), 1.23 (s, 6H)                                      |
| A-72         | 13.65 (s, 1H), 13.44 (s, 1H), 8.86 (s, 1H), 8.00 (m, 2H), 7.54 (m, 1H), 7.45 (m, 1H), 7.36 (m, 1H), 7.15 (m, 1H), 1.59 (s, 9H)                                      |
| A-73         | 13.43 (m, 2H), 8.80 (t, 1H), 8.02 (m, 2H), 7.48 (m, 2H), 7.33 (m, 1H), 7.17 (m, 1H), 3.49 (m, 2H), 1.98 (m, 1H), 0.98 (d, 6H)                                       |
| A-74         | 13.45 (m, 2H), 8.93 (d, 1H), 8.03 (m, 2H), 7.51 (m, 2H), 7.33 (m, 1H), 7.18 (m, 1H), 4.60 (m, 1H), 3.52 (d, 2H), 3.30 (s, 3H), 1.28 (d, 3H)                         |
| A-75         | 13.40 (m, 2H), 8.92 (t, 1H), 8.03 (m, 2H), 7.48 (m, 2H), 7.32 (m, 1H), 7.17 (m, 1H), 3.81 (m, 2H), 3.63 (m, 2H), 3.51 (m, 2H), 1.15 (t, 3H)                         |
| A-76         | 13.42 (m, 2H), 8.60 (d, 1H), 8.03 (m, 2H), 7.50 (m, 2H), 7.31 (m, 1H), 7.17 (m, 1H), 4.44 (m, 1H), 1.29 (d, 6H)                                                     |
| A-77         | 13.40 (m, 2H), 8.77 (t, 1H), 8.05 (m, 2H), 7.50 (m, 2H), 7.32 (m, 1H), 7.08 (m, 1H), 3.70 (m, 2H), 3.44 (m, 4H), 1.94 (m, 2H), 1.08 (m, 3H)                         |
| A-83         | 13.5 (s, 1H), 3.0 (s, 1H), 9.1 (t, 1H), 8.0 (m, 2H), 7.7 (dd, 1H), 7.5 (dd, 1H), 7.3 (d, 1H), 7.1 (t, 1H), 4.9 (s, 1H), 3.6 (d, 2H), 1.1 (d, 3H)                    |
| A-84         | 13.44 (s, 1H), 13.43 (s, 1H), 8.9 (d, 1H), 8.0 (m, 2H), 7.65 (d, 1H), 7.6 (d, 1H), 7.5 (dd, 1H), 7.2 (t, 1H), 4.6 (br t, 1H), 3.5 (d, 2H), 3.3 (s, 3H), 1.3 (d, 3H) |
| A-100        | 13.47 (s, 1H), 13.15 (s, 1H), 8.85 (s, 1H), 8.00 (m, 2H), 7.81 (m, 1H), 7.58 (m, 2H), 1.11 (s, 9H)                                                                  |
| A-101        | 13.18 (s, 1H), 13.13 (s, 1H), 8.76 (t, 1H), 8.04 (m, 2H), 7.81 (m, 1H), 7.61 (m, 2H), 3.48 (t, 2H), 1.98 (m, 1H), 0.98 (d, 6H)                                      |
| A-102        | 13.17 (s, 1H), 13.13 (s, 1H), 8.86 (t, 1H), 8.06 (m, 2H), 7.82 (d, 1H), 7.55 (m, 2H), 3.79 (m, 2H), 3.63 (m, 2H), 3.53 (m, 2H), 1.17 (t, 3H)                        |
| A-103        | 13.25 (s, 1H), 13.14 (s, 1H), 8.77 (d, 1H), 8.34 (m, 2H), 7.80 (d, 1H), 7.54 (m, 2H), 4.61 (m, 1H), 3.53 (d, 2H), 3.36 (s, 3H) 1.31 (d, 3H)                         |
| A-104        | 13.53 (s, 1H), 13.16 (s, 1H), 8.85 (s, 1H), 8.11 (m, 2H), 7.82 (d, 1H), 7.56 (m, 3H), 1.60 (s, 9H)                                                                  |
| A-105        | 13.21 (s, 1H), 13.15 (s, 1H), 8.77 (m, 1H), 8.12 (m, 2H), 7.84 (d, 1H), 7.60 (m, 3H), 3.49 (t, 2H), 2.00 (m, 1H), 0.99 (d, 6H)                                      |

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| Compound No. | <sup>1</sup> H NMR Resonance Data (δ)                                                                                                                      |
|--------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| A-106        | 13.24 (s, 1H), 13.15 (s, 1H), 8.86 (m, 1H), 8.13 (m, 2H), 7.82 (d, 1H), 7.62 (m, 2H), 7.51 (t, 1H), 3.79 (m, 2H), 3.64 (m, 2H), 3.53 (m, 2H), 1.17 (t, 3H) |
| A-107        | 13.30 (s, 1H), 13.14 (s, 1H), 8.77 (d, 1H), 8.12 (m, 2H), 7.81 (d, 1H), 7.53 (m, 3H), 4.60 (m, 1H), 3.53 (m, 2H), 3.36 (s, 3H), 1.31 (d, 3H)               |

**EXAMPLE 15**

[00264] Exemplary compounds described in above Examples were tested for activity against F<sub>1</sub>F<sub>0</sub>-ATPase by measuring the ability of the compounds to inhibit ATP synthesis. In addition, the compounds were assessed for cytotoxicity in Ramos cells. Results of the biological activity tests are shown in Table 4 below. Inhibition of F<sub>1</sub>F<sub>0</sub>-ATPase activity in synthesizing ATP and cytotoxicity in Ramos cells were measured according to the procedures described in K. M. Johnson *et al. Chemistry & Biology* **2005**, 12, 485-496. The symbol “NA” indicates that data was not available. In the column titled ATP Syn IC<sub>50</sub> in Table 4, the symbol “+” refers to an IC<sub>50</sub> >16 μm, “++” refers to an IC<sub>50</sub> from 5 to 16 μm, and “+++” refers to an IC<sub>50</sub> less than 5 μm. In the column titled Ramos Cell EC<sub>50</sub> in Table 4, the symbol “+” refers to an EC<sub>50</sub> >16 μm, “++” refers to an EC<sub>50</sub> from 5 to 16 μm, and “+++” refers to an EC<sub>50</sub> less than 5 μm. The detection limit of the assay measuring inhibition of F<sub>1</sub>F<sub>0</sub>-ATPase activity was IC<sub>50</sub> = 16 μM. The detection limit of the assay measuring cytotoxicity in Ramos cells was EC<sub>50</sub> = 16 μM.

**TABLE 4**

| Compound No. | ATP Syn IC <sub>50</sub> (μM) | Ramos Cell EC <sub>50</sub> (μM) |
|--------------|-------------------------------|----------------------------------|
| 1            | +++                           | +++                              |
| 2            | +++                           | +                                |
| 3            | +++                           | +++                              |
| 4            | +++                           | +++                              |
| 6            | ++                            | +                                |
| A-1          | +++                           | ++                               |
| A-2          | +++                           | +                                |
| A-3          | +++                           | ++                               |

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| Compound No. | ATP Syn IC <sub>50</sub> (μM) | Ramos Cell EC <sub>50</sub> (μM) |
|--------------|-------------------------------|----------------------------------|
| A-4          | +++                           | ++                               |
| A-5          | +++                           | +++                              |
| A-6          | +                             | +                                |
| A-7          | +                             | +++                              |
| A-8          | +++                           | +++                              |
| A-9          | +++                           | +++                              |
| A-10         | +++                           | +++                              |
| A-11         | +++                           | +++                              |
| A-12         | +++                           | +++                              |
| A-13         | +++                           | ++                               |
| A-14         | +++                           | +++                              |
| A-15         | +++                           | +++                              |
| A-16         | +++                           | ++                               |
| A-17         | +++                           | +                                |
| A-18         | +++                           | +                                |
| A-19         | +++                           | +++                              |
| A-20         | +++                           | +                                |
| A-21         | +++                           | ++                               |
| A-22         | +                             | +                                |
| A-23         | +++                           | ++                               |
| A-24         | +++                           | ++                               |
| A-25         | +++                           | ++                               |
| A-26         | ++                            | +                                |
| A-27         | +++                           | +                                |
| A-28         | ++                            | +                                |
| A-29         | +++                           | +                                |
| A-30         | +                             | +                                |
| A-31         | +++                           | +++                              |

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| Compound No. | ATP Syn IC <sub>50</sub> (μM) | Ramos Cell EC <sub>50</sub> (μM) |
|--------------|-------------------------------|----------------------------------|
| A-32         | +++                           | ++                               |
| A-33         | +                             | +                                |
| A-34         | ++                            | ++                               |
| A-35         | +                             | +                                |
| A-36         | +++                           | +++                              |
| A-37         | ++                            | +                                |
| A-38         | +                             | +                                |
| A-39         | ++                            | +                                |
| A-40         | +++                           | +++                              |
| A-41         | +++                           | +++                              |
| A-42         | +++                           | ++                               |
| A-43         | +                             | +                                |
| A-44         | +                             | +                                |
| A-45         | ++                            | +                                |
| A-46         | +                             | +                                |
| A-47         | +                             | +                                |
| A-48         | +                             | +                                |
| A-49         | +                             | +                                |
| A-50         | +++                           | +++                              |
| A-51         | +++                           | +++                              |
| A-52         | +++                           | +++                              |
| A-53         | +++                           | +                                |
| A-54         | +++                           | +                                |
| A-55         | +                             | +                                |
| A-56         | +++                           | +++                              |
| A-57         | +                             | ++                               |
| A-58         | ++                            | ++                               |

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| Compound No. | ATP Syn IC <sub>50</sub> (μM) | Ramos Cell EC <sub>50</sub> (μM) |
|--------------|-------------------------------|----------------------------------|
| A-59         | +                             | +                                |
| A-60         | ++                            | +                                |
| A-61         | +++                           | +++                              |
| A-62         | +                             | +                                |
| A-63         | +++                           | ++                               |
| A-64         | +++                           | +++                              |
| A-65         | +++                           | +++                              |
| A-66         | +++                           | +++                              |
| A-67         | +++                           | +++                              |
| A-68         | +++                           | +++                              |
| A-69         | +                             | +                                |
| A-70         | +                             | +                                |
| A-71         | +                             | +                                |
| A-72         | ++                            | +++                              |
| A-73         | ++                            | +++                              |
| A-74         | ++                            | ++                               |
| A-75         | +                             | +                                |
| A-76         | +++                           | +++                              |
| A-77         | ++                            | +++                              |
| A-78         | +++                           | +++                              |
| A-79         | +++                           | +++                              |
| A-80         | +++                           | +++                              |
| A-81         | +++                           | +++                              |
| A-82         | +++                           | +++                              |
| A-83         | +++                           | +++                              |
| A-84         | ++                            | +                                |
| A-85         | +++                           | +                                |

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| Compound No. | ATP Syn IC <sub>50</sub> (μM) | Ramos Cell EC <sub>50</sub> (μM) |
|--------------|-------------------------------|----------------------------------|
| A-86         | +                             | ++                               |
| A-87         | +                             | +                                |
| A-88         | +                             | +++                              |
| A-89         | ++                            | ++                               |
| A-90         | +                             | +                                |
| A-91         | ++                            | +                                |
| A-92         | ++                            | +++                              |
| A-93         | ++                            | ++                               |
| A-94         | +                             | ++                               |
| A-95         | +++                           | ++                               |
| A-96         | +++                           | +++                              |
| A-97         | +++                           | +++                              |
| A-98         | +++                           | +++                              |
| A-99         | +++                           | ++                               |
| A-100        | +++                           | +++                              |
| A-101        | +++                           | +++                              |
| A-102        | +++                           | +++                              |
| A-103        | +++                           | +++                              |
| A-104        | +++                           | +++                              |
| A-105        | +++                           | ++                               |
| A-106        | +++                           | +++                              |
| A-107        | +++                           | +++                              |
| A-108        | +++                           | ++                               |
| A-109        | ++                            | ++                               |
| A-110        | +++                           | ++                               |
| A-111        | +++                           | ++                               |
| A-112        | +++                           | +++                              |

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| Compound No. | ATP Syn $IC_{50}$ ( $\mu$ M) | Ramos Cell $EC_{50}$ ( $\mu$ M) |
|--------------|------------------------------|---------------------------------|
| A-113        | +                            | +                               |
| A-114        | +                            | +                               |
| A-115        | +                            | +                               |

### INCORPORATION BY REFERENCE

[00265] The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

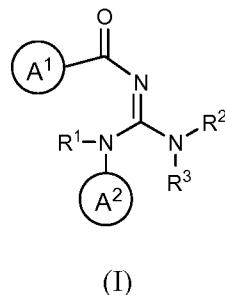
### EQUIVALENTS

5 [00266] 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 claims are intended to be embraced therein.

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**We Claim:**

1. A compound represented by Formula I:

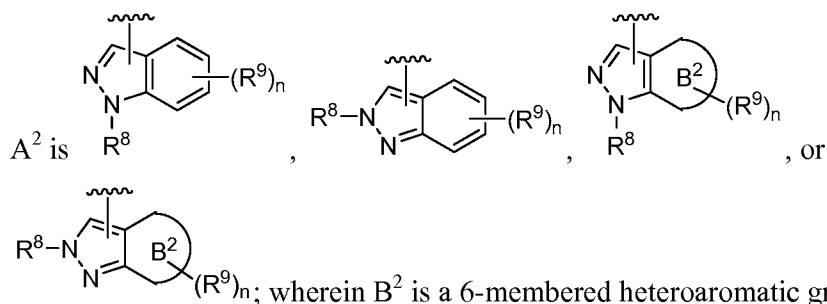


including all stereoisomers, geometric isomers, and tautomers; or a pharmaceutically acceptable salt or solvate of any of the foregoing; wherein:

A<sup>1</sup> is one of the following:

- (i) phenyl or a six-membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, cyano, -CO<sub>2</sub>R<sup>4</sup>, -C(O)R<sup>5</sup>, -S(O)R<sup>5</sup>, -SO<sub>2</sub>R<sup>5</sup>, -SO<sub>2</sub>N(R<sup>6</sup>)(R<sup>7</sup>), -C(O)N(R<sup>6</sup>)(R<sup>7</sup>), -N(R<sup>6</sup>)(R<sup>7</sup>), and -N(R<sup>4</sup>)C(O)(R<sup>5</sup>); or

- (ii) that is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, and C<sub>1</sub>-C<sub>6</sub>alkoxy; wherein B<sup>1</sup> is a 5-membered or 6-membered heterocycle;



R<sup>1</sup> and R<sup>2</sup> each represent independently hydrogen or alkyl;

R<sup>3</sup> is one of the following:

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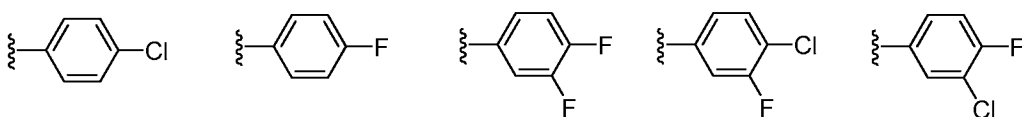
- 20 (i) alkyl optionally substituted with 1 or 2 substituents independently selected  
 21 from the group consisting of hydroxyl, alkoxy, -O-(C(R<sup>4</sup>)<sub>2</sub>)<sub>m</sub>-alkoxy,  
 22 -O-(C(R<sup>4</sup>)<sub>2</sub>)<sub>m</sub>-OH, -N(R<sup>6</sup>)(R<sup>7</sup>), cycloalkyl, heterocycloalkyl, -N(R<sup>6</sup>)C(O)R<sup>8</sup>,  
 23 -C(O)N(R<sup>6</sup>)(R<sup>7</sup>), -N(R<sup>6</sup>)C(O)N(R<sup>6</sup>)(R<sup>7</sup>), halogen, haloalkyl, and cyano; or  
 24 (ii) cycloalkyl or heterocycloalkyl, each of which is optionally substituted with  
 25 1, 2, or 3 substituents independently selected from the group consisting of  
 26 halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl, hydroxyalkyl, alkoxy,  
 27 -O-(C(R<sup>4</sup>)<sub>2</sub>)<sub>m</sub>-alkoxy, -O-(C(R<sup>4</sup>)<sub>2</sub>)<sub>m</sub>-OH, and cyano;  
 28 R<sup>4</sup> represents independently for each occurrence hydrogen, alkyl, or cycloalkyl; or two  
 29 occurrences of R<sup>4</sup> attached to the same carbon atom are taken together with said carbon atom to  
 30 form a saturated carbocyclic ring;  
 31 R<sup>5</sup> represents independently for each occurrence alkyl or cycloalkyl;  
 32 R<sup>6</sup> and R<sup>7</sup> each represent independently for each occurrence hydrogen, alkyl, or  
 33 cycloalkyl; or R<sup>6</sup> and R<sup>7</sup> are taken together with the nitrogen atom to which they are attached to  
 34 form a 3 to 7 membered heterocyclic ring optionally substituted with 1, 2, or 3 substituents  
 35 independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl,  
 36 cycloalkyl, and C<sub>1</sub>-C<sub>6</sub>alkoxy;  
 37 R<sup>8</sup> is hydrogen, or R<sup>8</sup> is alkyl substituted by hydroxyl, -N(H)(R<sup>6</sup>), heterocycloalkyl,  
 38 -N(H)C(O)R<sup>10</sup>, -C(O)N(H)(R<sup>6</sup>), or -N(H)C(O)N(R<sup>6</sup>)(R<sup>7</sup>);  
 39 R<sup>9</sup> represents independently for each occurrence halogen, haloalkyl, alkyl, cycloalkyl,  
 40 heterocycloalkyl, hydroxyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, or cyano;  
 41 R<sup>10</sup> is alkyl, cycloalkyl, aryl, or aralkyl; and  
 42 n is 0, 1, 2, 3, or 4; and  
 43 m is 1, 2, 3, 4, or 5.

- 1 2. The compound of claim 1, wherein A<sup>1</sup> is phenyl or a six-membered heteroaryl, each of  
 2 which is optionally substituted with 1, 2, or 3 substituents independently selected from the  
 3 group consisting of halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, and  
 4 C<sub>1</sub>-C<sub>6</sub>alkoxy.
- 1 3. The compound of claim 1, wherein A<sup>1</sup> is phenyl substituted with 1, 2, or 3 substituents  
 2 independently selected from the group consisting of halogen, haloalkyl, alkyl, and  
 3 hydroxyl.

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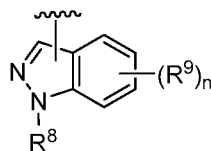
- 1 4. The compound of claim 1, wherein A<sup>1</sup> is phenyl substituted with 1 or 2 substituents  
 2 independently selected from the group consisting of chloro and fluoro.

- 1 5. The compound of claim 1, wherein A<sup>1</sup> is one of the following:

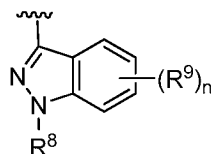


- 1 6. The compound of claim 1, wherein A<sup>1</sup> is a pyridinyl substituted with a 6-membered  
 2 heterocycloalkyl.

- 1 7. The compound of any one of claims 1-6, wherein A<sup>2</sup> is



- 1 8. The compound of any one of claims 1-6, wherein A<sup>2</sup> is



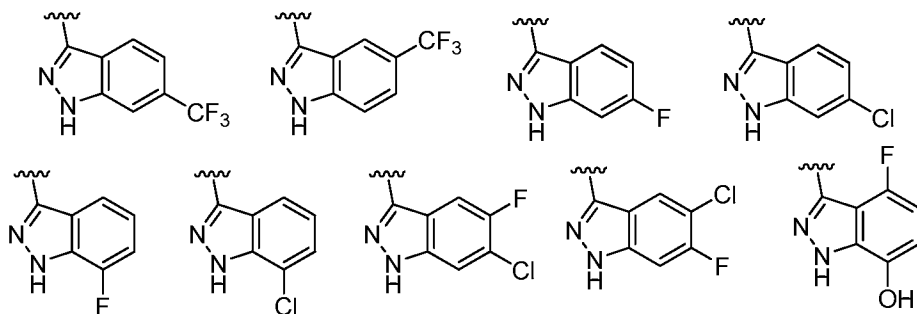
- 1 9. The compound of any one of claims 1-8, wherein R<sup>8</sup> is hydrogen.

- 1 10. The compound of any one of claims 1-9, wherein R<sup>9</sup> represents independently for each  
 2 occurrence halogen or haloalkyl.

- 1 11. The compound of any one of claims 1-9, wherein R<sup>9</sup> represents independently for each  
 2 occurrence chloro, fluoro, or trifluoromethyl.

- 1 12. The compound of any one of claims 1-11, wherein n is 1 or 2.

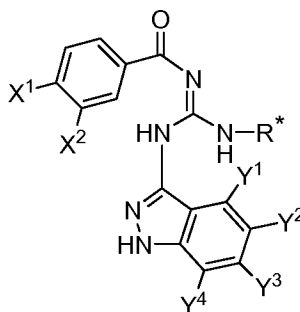
- 1 13. The compound of any one of claims 1-6, wherein A<sup>2</sup> is one of the following:



- 1 14. The compound of any one of claims 1-13, wherein R<sup>1</sup> and R<sup>2</sup> are hydrogen.

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- 1 15. The compound of any one of claims 1-14, wherein  $R^3$  is alkyl optionally substituted with 1  
 2 or 2 substituents independently selected from the group consisting of hydroxyl, alkoxy,  
 3  $-O-(C(R^4)_2)_m$ -alkoxy,  $-O-(C(R^4)_2)_m$ -OH,  $-N(R^6)(R^7)$ , and cycloalkyl.
- 1 16. The compound of any one of claims 1-14, wherein  $R^3$  is alkyl or cycloalkyl.
- 1 17. The compound of any one of claims 1-14, wherein  $R^3$  is cyclobutyl, cyclopentyl,  
 2 cyclohexyl, or  $C_{2-6}$  alkyl.
- 1 18. The compound of any one of claims 1-14, wherein  $R^3$  is  $C_{1-6}$  alkyl substituted by  $C_{1-6}$   
 2 alkoxy.
- 1 19. The compound of any one of claims 1-18, wherein  $R^4$  represents independently for each  
 2 occurrence hydrogen or methyl.
- 1 20. The compound of any one of claims 1-19, wherein  $R^5$  is methyl.
- 1 21. The compound of any one of claims 1-20, wherein  $R^6$  and  $R^7$  are hydrogen.
- 1 22. The compound of claim 1, wherein said compound is represented by Formula I-A1:



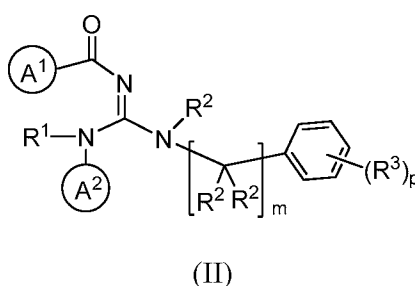
(I-A1)

4 including all stereoisomers, geometric isomers, and tautomers; or a pharmaceutically  
 5 acceptable salt or solvate of any of the foregoing; wherein:

- 6  $X^1$  and  $X^2$  each represent independently hydrogen, chloro, fluoro, or  $-CF_3$ ;
- 7  $Y^1$ ,  $Y^2$ ,  $Y^3$ , and  $Y^4$  each represent independently hydrogen, chloro, fluoro, hydroxyl, or  
 8  $-CF_3$ ; and
- 9  $R^*$  is one of the following:
- 10 (i) alkyl optionally substituted with 1 or 2 substituents independently selected  
 11 from the group consisting of hydroxyl, alkoxy, and cycloalkyl; or

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- 12 (ii) cycloalkyl optionally substituted with 1 or 2 substituents independently  
 13 selected from the group consisting of hydroxyl, alkyl, hydroxyalkyl, and  
 14 alkoxy.
- 1 23. The compound of claim 22, wherein  $X^1$  and  $X^2$  are each independently chloro or fluoro.
- 1 24. The compound of claim 22 or 23, wherein  $Y^1$ ,  $Y^2$ , and  $Y^4$  are hydrogen; and  $Y^3$  is fluoro or  
 2  $-CF_3$ .
- 1 25. The compound of claim 22 or 23, wherein  $Y^1$  and  $Y^4$  are hydrogen; and  $Y^2$  and  $Y^3$  are each  
 2 independently fluoro or  $-CF_3$ .
- 1 26. The compound of any one of claims 22-25, wherein  $R^*$  is alkyl optionally substituted with 1  
 2 or 2 substituents independently selected from the group consisting of hydroxyl, alkoxy, and  
 3 cycloalkyl.
- 1 27. The compound of any one of claims 22-25, wherein  $R^*$  is alkyl or cycloalkyl.
- 1 28. The compound of any one of claims 22-25, wherein  $R^*$  is cyclobutyl, cyclopentyl,  
 2 cyclohexyl, or  $C_{2-6}$  alkyl.
- 1 29. The compound of any one of claims 22-25, wherein  $R^*$  is  $C_{1-6}$  alkyl substituted by  $C_{1-6}$   
 2 alkoxy.
- 1 30. A compound represented by Formula II:



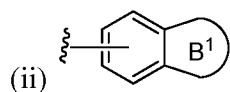
4 including all stereoisomers, geometric isomers, and tautomers; or a pharmaceutically  
 5 acceptable salt or solvate of any of the foregoing; wherein:

6  $A^1$  is one of the following:

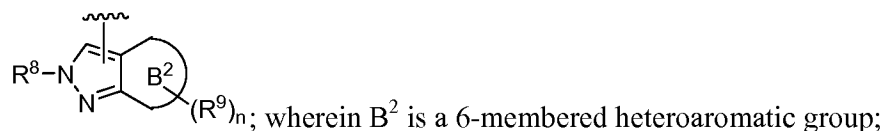
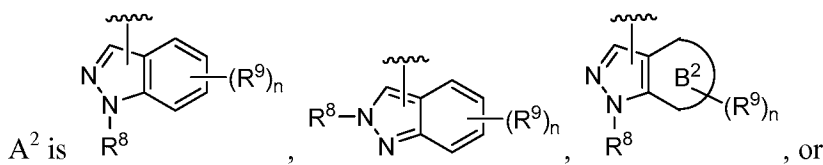
- 7 (i) phenyl or a six-membered heteroaryl, each of which is optionally substituted  
 8 with 1, 2, or 3 substituents independently selected from the group consisting of  
 9 halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl,  $C_1$ - $C_6$ alkoxy,

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cyano,  $-\text{CO}_2\text{R}^4$ ,  $-\text{C}(\text{O})\text{R}^5$ ,  $-\text{S}(\text{O})\text{R}^5$ ,  $-\text{SO}_2\text{R}^5$ ,  $-\text{SO}_2\text{N}(\text{R}^6)(\text{R}^7)$ ,  $-\text{C}(\text{O})\text{N}(\text{R}^6)(\text{R}^7)$ ,  
 $-\text{N}(\text{R}^6)(\text{R}^7)$ , and  $-\text{N}(\text{R}^4)\text{C}(\text{O})(\text{R}^5)$ ; or



that is optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, and  $\text{C}_1\text{-C}_6$ alkoxy; wherein  $\text{B}^1$  is a 5-membered or 6-membered heterocycle;



$\text{R}^1$  is hydrogen or alkyl;

$\text{R}^2$  represents independently for each occurrence hydrogen or alkyl;

$\text{R}^3$  represents independently for each occurrence halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyalkyl,  $\text{C}_1\text{-C}_6$ alkoxy, or cyano;

$\text{R}^4$  represents independently for each occurrence hydrogen, alkyl, or cycloalkyl; or two occurrences of  $\text{R}^4$  attached to the same carbon atom are taken together with said carbon atom to form a saturated carbocyclic ring;

$\text{R}^5$  represents independently for each occurrence alkyl or cycloalkyl;

$\text{R}^6$  and  $\text{R}^7$  each represent independently for each occurrence hydrogen, alkyl, or cycloalkyl; or  $\text{R}^6$  and  $\text{R}^7$  are taken together with the nitrogen atom to which they are attached to form a 3 to 7 membered heterocyclic ring optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl, and  $\text{C}_1\text{-C}_6$ alkoxy;

$\text{R}^8$  is hydrogen, or  $\text{R}^8$  is alkyl substituted by hydroxyl,  $-\text{N}(\text{H})(\text{R}^6)$ , heterocycloalkyl,  $-\text{N}(\text{H})\text{C}(\text{O})\text{R}^{10}$ ,  $-\text{C}(\text{O})\text{N}(\text{H})(\text{R}^6)$ , or  $-\text{N}(\text{H})\text{C}(\text{O})\text{N}(\text{R}^6)(\text{R}^7)$ ;

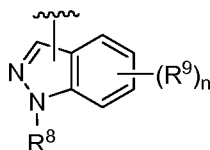
$\text{R}^9$  represents independently for each occurrence halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl,  $\text{C}_1\text{-C}_6$ alkoxy, or cyano;

$\text{R}^{10}$  is alkyl, cycloalkyl, aryl, or aralkyl;

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36 n is 0, 1, 2, 3, or 4;

37 m and p each represent independently 0, 1, 2, or 3; and

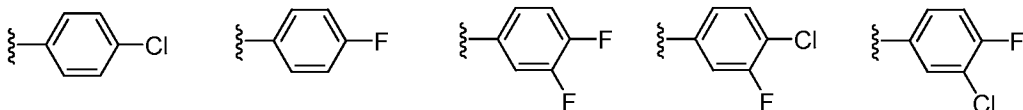


38 provided that if A<sup>2</sup> is  and R<sup>3</sup> is halogen or haloalkyl, then n is 1, 2 or  
39 3.

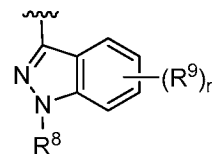
1 31. The compound of claim 30, wherein A<sup>1</sup> is phenyl substituted with 1, 2, or 3 substituents  
2 independently selected from the group consisting of halogen, haloalkyl, alkyl, and  
3 hydroxyl.

1 32. The compound of claim 30, wherein A<sup>1</sup> is phenyl substituted with 1 or 2 substituents  
2 independently selected from the group consisting of chloro, fluoro, and trifluoromethyl.

1 33. The compound of claim 30, wherein A<sup>1</sup> is one of the following:



1 34. The compound of any one of claims 30-33, wherein A<sup>2</sup> is  .



1 35. The compound of any one of claims 30-33, wherein A<sup>2</sup> is  .

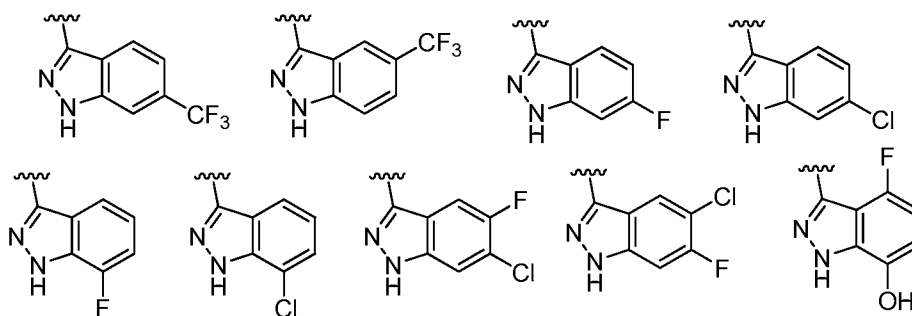
1 36. The compound of any one of claims 30-35, wherein R<sup>9</sup> represents independently for each  
2 occurrence chloro, fluoro, or trifluoromethyl.

1 37. The compound of any one of claims 30-36, wherein n is 1 or 2.

1 38. The compound of any one of claims 30-37, wherein R<sup>8</sup> is hydrogen.

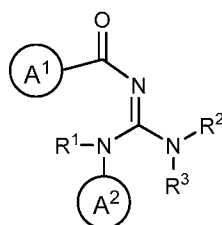
1 39. The compound of any one of claims 30-33, wherein A<sup>2</sup> is one of the following:

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2

- 1 40. The compound of any one of claims 30-39, wherein  $R^1$  and  $R^2$  are hydrogen.
- 1 41. The compound of any one of claims 30-40, wherein  $R^3$  is halogen or haloalkyl.
- 1 42. The compound of any one of claims 30-40, wherein  $R^3$  is chloro or fluoro.
- 1 43. The compound of any one of claims 30-42, wherein  $R^4$  represents independently for each  
2 occurrence hydrogen or methyl,  $R^5$  is methyl, and  $R^6$  and  $R^7$  are hydrogen.
- 1 44. The compound of any one of claims 30-43, wherein  $m$  is 0.
- 1 45. The compound of any one of claims 30-43, wherein  $m$  is 1.
- 1 46. The compound of any one of claims 30-45, wherein  $p$  is 1 or 2.
- 1 47. A compound represented by Formula III:



2

3

(III)

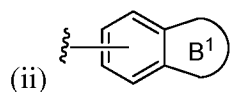
4 including all stereoisomers, geometric isomers, and tautomers; or a pharmaceutically  
5 acceptable salt or solvate of any of the foregoing; wherein:

6  $A^1$  is one of the following:

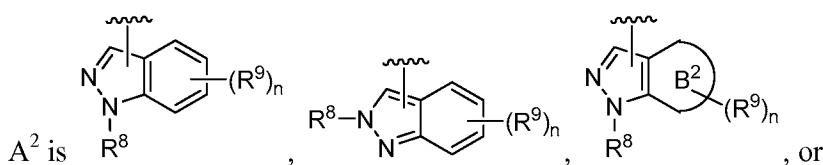
- 7 (i) phenyl or a six-membered heteroaryl, each of which is optionally substituted  
8 with 1, 2, or 3 substituents independently selected from the group consisting of  
9 halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl,  $C_1$ - $C_6$ alkoxy,

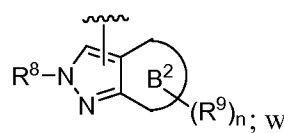
- 123 -

cyano,  $-\text{CO}_2\text{R}^4$ ,  $-\text{C}(\text{O})\text{R}^5$ ,  $-\text{S}(\text{O})\text{R}^5$ ,  $-\text{SO}_2\text{R}^5$ ,  $-\text{SO}_2\text{N}(\text{R}^6)(\text{R}^7)$ ,  $-\text{C}(\text{O})\text{N}(\text{R}^6)(\text{R}^7)$ ,  
 $-\text{N}(\text{R}^6)(\text{R}^7)$ , and  $-\text{N}(\text{R}^4)\text{C}(\text{O})(\text{R}^5)$ ; or



that is optionally substituted with 1 or 2 substituents  
independently selected from the group consisting of halogen, haloalkyl, alkyl,  
cycloalkyl, heterocycloalkyl, hydroxyl, and  $\text{C}_1\text{-C}_6$ alkoxy; wherein  $\text{B}^1$  is a 5-  
membered or 6-membered heterocycle;



; wherein  $\text{B}^2$  is a 6-membered heteroaromatic group;

$\text{R}^1$  and  $\text{R}^2$  each represent independently hydrogen or alkyl;

$\text{R}^3$  is one of the following:

- (i) alkyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of hydroxyl, alkoxy,  $-\text{O}-(\text{C}(\text{R}^4)_2)_m\text{-alkoxy}$ ,  $-\text{O}-(\text{C}(\text{R}^4)_2)_m\text{-OH}$ ,  $-\text{N}(\text{R}^6)(\text{R}^7)$ , cycloalkyl, heterocycloalkyl,  $-\text{N}(\text{R}^6)\text{C}(\text{O})\text{R}^8$ ,  $-\text{C}(\text{O})\text{N}(\text{R}^6)(\text{R}^7)$ ,  $-\text{N}(\text{R}^6)\text{C}(\text{O})\text{N}(\text{R}^6)(\text{R}^7)$ , halogen, haloalkyl, and cyano; or
- (ii) cycloalkyl or heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl, hydroxyalkyl, alkoxy,  $-\text{O}-(\text{C}(\text{R}^4)_2)_m\text{-alkoxy}$ ,  $-\text{O}-(\text{C}(\text{R}^4)_2)_m\text{-OH}$ , and cyano;

$\text{R}^4$  represents independently for each occurrence hydrogen, alkyl, or cycloalkyl; or two occurrences of  $\text{R}^4$  attached to the same carbon atom are taken together with said carbon atom to form a saturated carbocyclic ring;

$\text{R}^5$  represents independently for each occurrence alkyl or cycloalkyl;

$\text{R}^6$  and  $\text{R}^7$  each represent independently for each occurrence hydrogen, alkyl, or cycloalkyl; or  $\text{R}^6$  and  $\text{R}^7$  are taken together with the nitrogen atom to which they are attached to form a 3 to 7 membered heterocyclic ring optionally substituted with 1, 2, or 3 substituents

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independently selected from the group consisting of halogen, haloalkyl, hydroxyl, alkyl, cycloalkyl, and C<sub>1</sub>-C<sub>6</sub>alkoxy;

R<sup>8</sup> is alkyl, -CH<sub>2</sub>-S-alkyl, -CO<sub>2</sub>-alkylene-Z, -CO<sub>2</sub>-alkyl, or -C(O)-alkyl optionally substituted by one or more of hydroxyl, halogen, and -N(R<sup>6</sup>)(R<sup>7</sup>);

R<sup>9</sup> represents independently for each occurrence halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, C<sub>1</sub>-C<sub>6</sub>alkoxy, or cyano;

Z is -O-P(O)(OH)<sub>2</sub>, -OC(O)-arylene-alkylene-O-P(O)(OH)<sub>2</sub>, -OC(O)-arylene-O-P(O)(OH)<sub>2</sub>, or -OC(O)-alkylene-O-P(O)(OH)<sub>2</sub>;

n is 0, 1, 2, 3, or 4; and

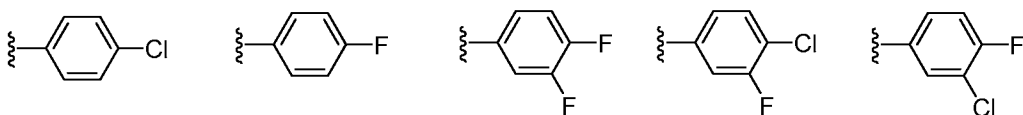
m is 1, 2, 3, 4, or 5.

48. The compound of claim 47, wherein A<sup>1</sup> is phenyl or a six-membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, cycloalkyl, heterocycloalkyl, hydroxyl, and C<sub>1</sub>-C<sub>6</sub>alkoxy.

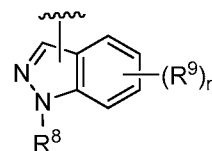
49. The compound of claim 47, wherein A<sup>1</sup> is phenyl substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen, haloalkyl, alkyl, and hydroxyl.

50. The compound of claim 47, wherein A<sup>1</sup> is phenyl substituted with 1 or 2 substituents independently selected from the group consisting of chloro and fluoro.

51. The compound of claim 47, wherein A<sup>1</sup> is one of the following:

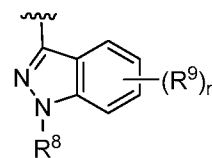


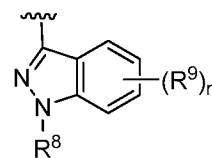
52. The compound of claim 47, wherein A<sup>1</sup> is a pyridinyl substituted with a 6-membered heterocycloalkyl.

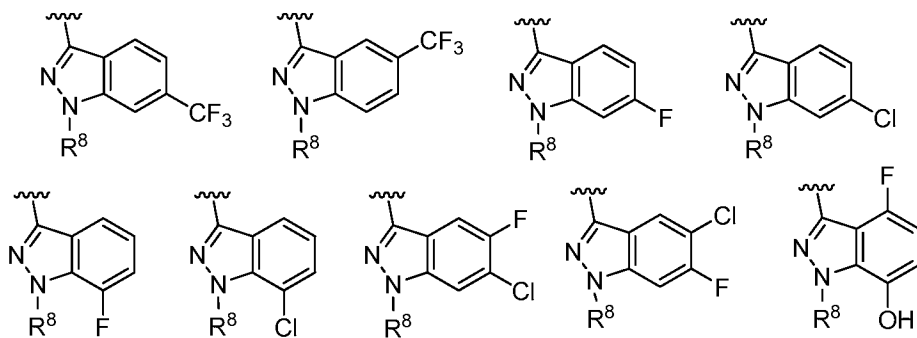


53. The compound of any one of claims 47-52, wherein A<sup>2</sup> is

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- 1 54. The compound of any one of claims 47-52, wherein A<sup>2</sup> is .
- 1 55. The compound of any one of claims 47-54, wherein R<sup>9</sup> represents independently for each  
2 occurrence halogen or haloalkyl.
- 1 56. The compound of any one of claims 47-54, wherein R<sup>9</sup> represents independently for each  
2 occurrence chloro, fluoro, or trifluoromethyl.
- 1 57. The compound of any one of claims 47-56, wherein n is 1 or 2.
- 1 58. The compound of any one of claims 47-52, wherein A<sup>2</sup> is one of the following:



- 1 59. The compound of any one of claims 47-58, wherein R<sup>1</sup> and R<sup>2</sup> are hydrogen.
- 1 60. The compound of any one of claims 47-59, wherein R<sup>3</sup> is alkyl optionally substituted with 1  
2 or 2 substituents independently selected from the group consisting of hydroxyl, alkoxy,  
3 -O-(C(R<sup>4</sup>)<sub>2</sub>)<sub>m</sub>-alkoxy, -O-(C(R<sup>4</sup>)<sub>2</sub>)<sub>m</sub>-OH, -N(R<sup>6</sup>)(R<sup>7</sup>), and cycloalkyl.
- 1 61. The compound of any one of claims 47-59, wherein R<sup>3</sup> is alkyl or cycloalkyl.
- 1 62. The compound of any one of claims 47-59, wherein R<sup>3</sup> is cyclobutyl, cyclopentyl,  
2 cyclohexyl, or C<sub>2-6</sub> alkyl.
- 1 63. The compound of any one of claims 47-59, wherein R<sup>3</sup> is C<sub>1-6</sub> alkyl substituted by C<sub>1-6</sub>  
2 alkoxy.
- 1 64. The compound of any one of claims 47-63, wherein R<sup>4</sup> represents independently for each  
2 occurrence hydrogen or methyl.
- 1 65. The compound of any one of claims 47-64, wherein R<sup>5</sup> is methyl.

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- 1 66. The compound of any one of claims 47-65, wherein R<sup>6</sup> and R<sup>7</sup> are hydrogen.
- 1 67. The compound of any one of claims 47-66, wherein R<sup>8</sup> is -CO<sub>2</sub>-alkylene-Z.
- 1 68. The compound of any one of claims 47-67, wherein Z is -O-P(O)(OH)<sub>2</sub>,
- 1 69. A compound listed in any one of Tables 1-4 or a pharmaceutically acceptable salt thereof.
- 1 70. A pharmaceutical composition comprising a compound of any one of claims 1-69 and a  
2 pharmaceutically acceptable carrier.
- 1 71. A method of treating a disorder selected from the group consisting of an immune disorder,  
2 inflammatory disorder, cardiovascular disease, myeloma, lymphoma, cancer, and bacterial  
3 infection, comprising administering to a patient in need thereof a therapeutically effective  
4 amount of a compound of any one of claims 1-69 in order to ameliorate a symptom of the  
5 disorder.
- 1 72. The method of claim 71, wherein the disorder is rheumatoid arthritis, psoriasis, chronic  
2 graft-versus-host disease, acute graft-versus-host disease, Crohn's disease, inflammatory  
3 bowel disease, multiple sclerosis, systemic lupus erythematosus, Celiac Sprue, idiopathic  
4 thrombocytopenic thrombotic purpura, myasthenia gravis, Sjogren's syndrome,  
5 scleroderma, ulcerative colitis, asthma, uveitis, or epidermal hyperplasia.
- 1 73. The method of claim 71, wherein the disorder is cartilage inflammation, bone degradation,  
2 arthritis, juvenile arthritis, juvenile rheumatoid arthritis, pauciarticular juvenile rheumatoid  
3 arthritis, polyarticular juvenile rheumatoid arthritis, systemic onset juvenile rheumatoid  
4 arthritis, juvenile ankylosing spondylitis, juvenile enteropathic arthritis, juvenile reactive  
5 arthritis, juvenile Reter's Syndrome, SEA Syndrome, juvenile dermatomyositis, juvenile  
6 psoriatic arthritis, juvenile scleroderma, juvenile systemic lupus erythematosus, juvenile  
7 vasculitis, pauciarticular rheumatoid arthritis, polyarticular rheumatoid arthritis, systemic  
8 onset rheumatoid arthritis, ankylosing spondylitis, enteropathic arthritis, reactive arthritis,  
9 Reter's Syndrome, dermatomyositis, psoriatic arthritis, vasculitis, myolitis, polymyolitis,  
10 dermatomyolitis, osteoarthritis, polyarteritis nodossa, Wegener's granulomatosis, arteritis,  
11 polymyalgia rheumatica, sarcoidosis, sclerosis, primary biliary sclerosis, sclerosing  
12 cholangitis, dermatitis, atopic dermatitis, atherosclerosis, Still's disease, chronic obstructive  
13 pulmonary disease, Guillain-Barre disease, Type I diabetes mellitus, Graves' disease,  
14 Addison's disease, Raynaud's phenomenon, or autoimmune hepatitis.

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- 1    74. The method of any one of claims 71-73, wherein the patient is a human.
- 1    75. A method of inhibiting a  $F_1F_0$ -ATPase, comprising exposing a  $F_1F_0$ -ATPase to a compound  
2        of any one of claims 1-69 to inhibit said  $F_1F_0$ -ATPase.
- 1    76. The method of claim 75, wherein the  $F_1F_0$ -ATPase is mitochondrial  $F_1F_0$ -ATPase.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US13/44734

| <b>A. CLASSIFICATION OF SUBJECT MATTER</b><br>IPC(8) - A61K 31/155; A61P 9/00; C07D 231/54 (2013.01)<br>USPC - 514/94, 359, 394<br>According to International Patent Classification (IPC) or to both national classification and IPC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                               |                                                                                                                                    |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| <b>B. FIELDS SEARCHED</b><br>Minimum documentation searched (classification system followed by classification symbols)<br>IPC(8): A61K 31/155; A61P 9/00; C07D 231/54 (2013.01)<br>USPC: 514/94, 359, 394, 403, 447<br>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched<br>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)<br>MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); DialogPRO; Google Scholar; IP.com; guanidin*, F1F0, ATPhydrol*, ATPas*, inhibit*, modulat*, regulat*, indazol*, benzpyrazol*, isindazon*, composition*, carrier*, cardio*, diseas*, cancer*, tumor*, atherosclero*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                               |                                                                                                                                    |
| <b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                               |                                                                                                                                    |
| Category*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Citation of document, with indication, where appropriate, of the relevant passages                                                                                            | Relevant to claim No.                                                                                                              |
| Y                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | US 2004/0039033 A1 (ATWAL, KS et al.) 26 February 2004; abstract; paragraphs [0002], [0011]-[0025], [0028]-[0029], [0049]-[0051], [0053]-[0054], [0056]-[0059], [0065]-[0066] | 1-6, 7/1-6, 8/1-6, 13/1-6, 22-23, 24/22-23, 25/22-23, 30-33, 34/30-33, 35/30-33, 39/30-33, 47-52, 53/47-52, 54/47-52, 58/47-52, 69 |
| Y                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | WO 2010/030891 A2 (GLICK, GD et al.) 18 March 2010; page 54, lines 1-19; page 55, lines 6-13                                                                                  | 1-6, 7/1-6, 8/1-6, 13/1-6, 22-23, 24/22-23, 25/22-23, 30-33, 34/30-33, 35/30-33, 39/30-33, 47-52, 53/47-52, 54/47-52, 58/47-52, 69 |
| A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | WO 2003/050261 A2 (ATWAL, KS et al.) 19 June 2003; page 3, lines 20-23; page 4, lines 13-25; page 5, lines 1-19; page 6, lines 5-13                                           | 1-6, 7/1-6, 8/1-6, 13/1-6, 22-23, 24/22-23, 25/22-23, 30-33, 34/30-33, 35/30-33, 39/30-33, 47-52, 53/47-52, 54/47-52, 58/47-52, 69 |
| <input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                               |                                                                                                                                    |
| * Special categories of cited documents:<br>"A" document defining the general state of the art which is not considered to be of particular relevance<br>"E" earlier application or patent but published on or after the international filing date<br>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)<br>"O" document referring to an oral disclosure, use, exhibition or other means<br>"P" document published prior to the international filing date but later than the priority date claimed<br>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention<br>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone<br>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art<br>"&" document member of the same patent family |                                                                                                                                                                               |                                                                                                                                    |
| Date of the actual completion of the international search<br>11 November 2013 (11.11.2013)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                               | Date of mailing of the international search report<br>20 NOV 2013                                                                  |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                               | Authorized officer:<br>Shane Thomas<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774                                         |

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US13/44734

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

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

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3. ☒ Claims Nos.: 9-12, 14-21, 26-29, 36-38, 40-46, 55-57, 59-68, 70-76  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.